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BLOOD STUDIES IN ALLERGY*

V. Variation of Leukocytes Following Test Feeding of Foods: Appraisal of the Individual Food Test

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ALTHOUGH Vaughan[15] suggested the leukopenic index as a diagnostic aid in food allergy in April 1934, Rinkel had reported the results of clinical observations following the trial feeding of foods the preceding November (1933). Rinkel[10] subsequently included pre-ingestion and post-ingestion total leukocyte determinations as a part of his technique but continued to stress the diagnostic significance of clinical reactions developed during and following experimental feeding. As the result of more than a decade of observations of food sensitive patients in varying phases of clinical tolerance and intolerance in respect to the specific food tested, Rinkel[11] recently reported a further improvement in the method. This consists of the preliminary preparation of the patient by the complete avoidance of the food in question for four days prior to testing, and the feeding of a second dose an hour after the first if clinical symptoms are not produced during the first hour.

Squier and Madison[14], employing a diluting fluid of eosin and acetone in distilled water which permits the enumeration of eosin-staining cells in the counting chamber, reported an increase of the cells taking the eosin stain in addition to a leukopenia following the test feeding of an allergenic food. Their method has not come into general use, presumably, because it does not permit a quantitative enumeration of either the true eosinophils or the total leukocytes, due to the rapid fading of all cells in the presence of a hypotonic diluent. However, if serial determinations are made at a

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constant interval from the time of diluting the blood sample, the fading of cells appears to occur at a constant rate following the ingestion of a compatible food. A more rapid "disappearance" of white blood cells following the ingestion of an allergenic food suggests an increased fragility of these cells in addition to the actual leukopenia described by others. For these reasons the ingestion test as employed by Squier does not reveal the same information as does Rinkel's technique or the method originally described by Vaughan. However, in expert hands Squier's and Addison's method is a valuable adjunct in the recognition of specific food reactions. The technical aspects of this procedure have been discussed in greater detail elsewhere.[5]

After the development of a white blood cell-diluting fluid of equal parts propylene glycol and water containing phloxine and methylene blue, it seemed desirable to study the hematological aspects of the food and drug response since this method permits an accurate enumeration of eosinophils in the counting chamber in the same sample of blood employed in counting the total leukocytes. The hematologic changes following the trial ingestion of sulfonamide drugs in cases of known sensitivity, and the variation of eosinophils associated with test feeding of allergenic foods, have been described.[5,7] Although a delayed eosinophilia was observed in both instances, this response was inconstant in food allergy; its delayed occurrence does not favor eosinophil measurements as a possible diagnostic method useful in detecting specific sensitivity.

In starting the present study of the total leukocyte response following the trial ingestion of foods, individuals of known sensitivity were first fed the specific allergen in the fasting condition without reference to its inclusion or omission in the preceding diet. Under these circumstances we often obtained hematologic responses which, according to the early reports of Vaughan and others, were at variance with the clinical histories. We then learned that we were testing patients in various phases of specific allergic tolerance, for, as a rule, the cases of known sensitivity had been avoiding the suspected food either partially or completely for some time prior to the test. For instance, we observed several cases of unquestioned clinical sensitivity where the specific agent had been avoided for several weeks or months, in whom trial ingestion of a single dose was not followed by a leukopenia or the production of symptoms. Other instances in which the food in question had been eaten daily prior to the test did not respond with as concise a clinical or hematologic reaction as when re-tested after four days of specific avoidance. In still other instances we apparently missed an early leukopenia in spite of precipitating acute allergic symptoms by performing the postprandial blood counts at intervals of every thirty minutes.

In late 1943 we adopted a technique patterned after Rinkel's[11] individual food test. Only cases of uncontrolled clinical allergy with unknown food sensitivities were used. The food to be tested had been included in the

diet until four days prior to the test, then it was completely avoided for four days and tested on the fifth. All food, medications and tobacco were omitted for at least five hours prior to the test. After resting in the sitting position for thirty minutes, two total leukocyte counts were made to establish a base line. An average to a large serving of the food to be tested was eaten within a period of five minutes and total leukocyte determinations were made at intervals of twenty, forty and sixty minutes after completion of the test meal. If symptoms had not been produced within the first hour after test feeding, a second serving was fed and the patient was kept under clinical observation for an additional thirty minutes.

The total leukocytes of eight squares or the four corners of each side of the counting chamber were counted. Each serial observation was made by the same technician employing the same pipette and counting chamber. The average of two pre-ingestion total leukocyte counts was taken as the fasting level, and only in this respect did the mechanics of the technique differ from that recently advocated by Rinkel.[11] In the graphic representation of results we have found it advantageous to plot the postingestion variation in total leukocytes in terms of percentage rather than numerical deviation from the pre-ingestion level. As a time-saving measure in the calculation of the percentage variation, the increment or decrement percentage may be read directly from a chart.[6] All patients were kept under close clinical observation throughout the test. Pulse and blood pressure determinations as outlined by Rinkel were not performed routinely.

Since applying this procedure as a diagnostic measure in cases of unknown food sensitivity there has been a high degree of correlation between the findings of a postprandial leukocytosis and the current evidence of specific clinical tolerance on the one hand, and a postingestion leukopenia with evidence of clinical intolerance following test or cumulative feeding on the other hand.

THE INTERPRETATION OF INDIVIDUAL FOOD TESTS

Vaughan originally suggested that the diminution of 1,000 cells from the fasting level occurring after the ingestion of a food indicated an incompatible blood response. Under certain circumstances, Rinkel and Gay[12] found a decrease of 500 cells to occur in association with clinical evidence of intolerance. From an analysis of cases of proved clinical sensitivity, our experience indicates that a postingestion leukopenia of greater numerical magnitude may be expected in cases having a high basal total leukocyte count, and, conversely, lesser degrees of leukopenia as measured in absolute values occur in cases having a relatively low initial white blood cell level. Particularly in the latter group, acute allergic manifestations may develop after the trial feeding of a food accompanied by a decrease of the total leukocyte count between 500 and 1,000 cells. For these reasons we have found it more satisfactory to express the leukopenia or the leukocy-

tosis in terms of the percentage deviation from the fasting level rather than to employ the numerical expression originated by Vaughan and continued by Rinkel. This method of graphic representation has the further

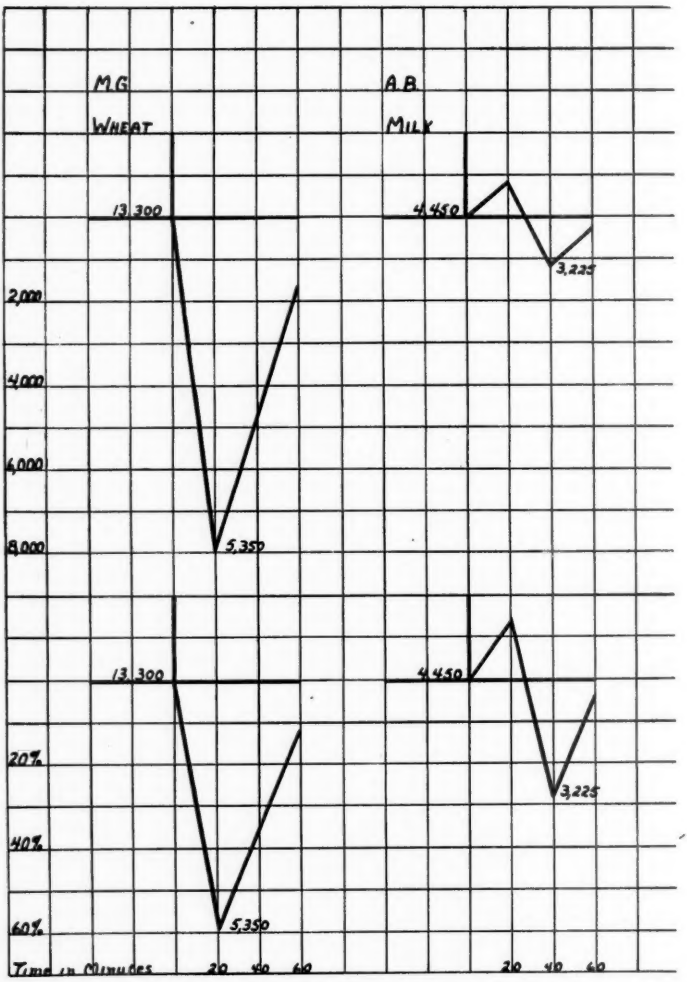

Fig. 1. Methods of plotting the results of individual food tests. Post-ingestive total leukocyte counts plotted according to the numerical deviation from the pre-ingestion level (above), and according to the percentage deviation (below).

advantage that it minimizes the variations occurring from high basal counts and magnifies those arising from an initial low total leukocyte level. These points are illustrated in Figure 1, which shows the test data of

two cases plotted by each method. Although in the first case there was a profound leukopenia, a single feeding failed to produce immediate or delayed symptoms, in contrast to the acute clinical reaction occurring in the second instance in the presence of a minimal blood change.

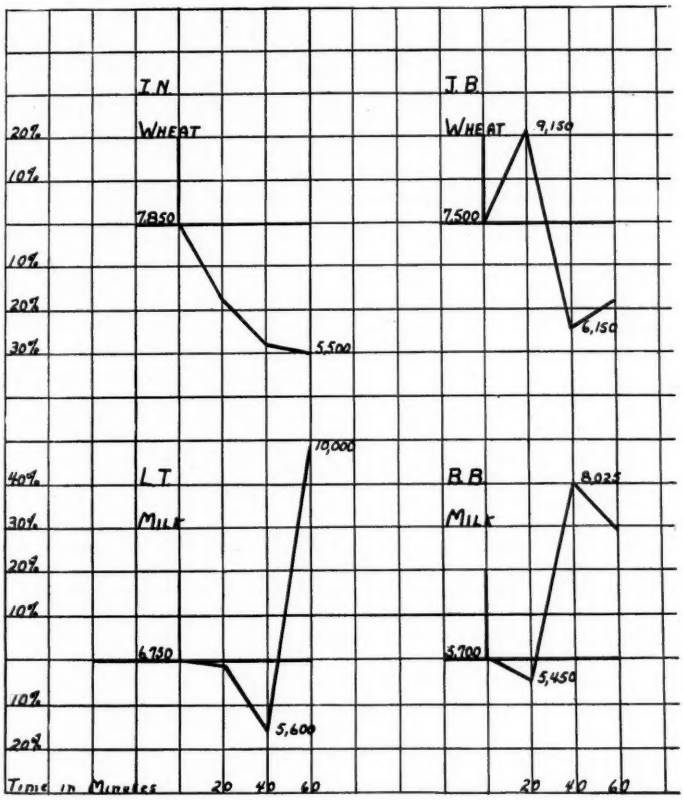

Fig. 2. Instances of positive individual food tests associated with sharp clinical reactions showing abrupt changes in the post-ingestive total leukocyte counts.

We wish to emphasize the importance of the graphic representation of test data; it should always be done before attempting to interpret the results of a given test. One learns by experience to recognize certain patterns of plotted results which are commonly associated with severe reactions. This was pointed out by Rinkel, as well as the fact that sudden changes in the leukocyte level are commonly associated with more severe reactions. Instances of this type are illustrated in Figure 2. Graph 1 of this figure is that of a patient with perennial allergic rhinitis and bronchial asthma who developed mucus in her throat five minutes after the ingestion

of wheat, followed by complete nasal obstruction beginning at ten minutes. Graph 2 is from a patient with perennial allergic rhinitis, gastro-intestinal allergy and allergic headache, who developed a severe headache with dizziness thirty minutes after feeding with wheat. Graph 3 is from a case of

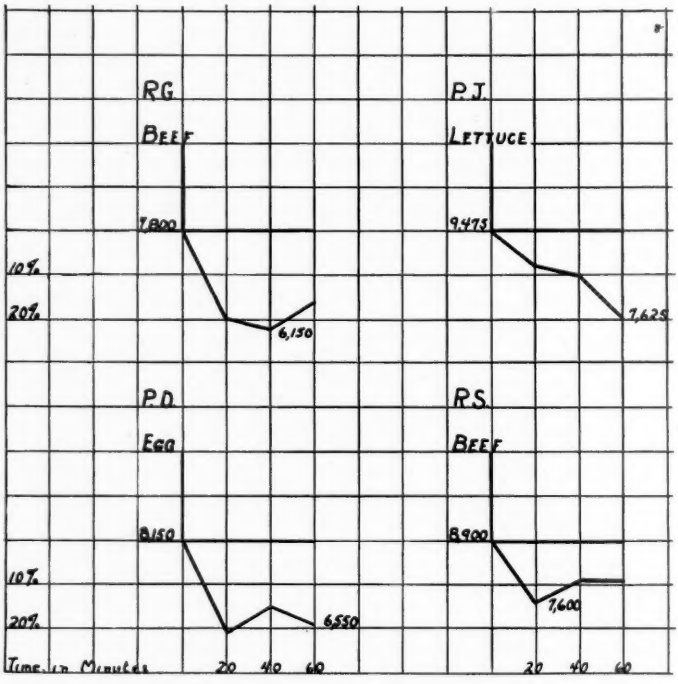

Fig. 3. Instances of positive individual food tests associated with clinical reactions illustrative of commonly encountered blood responses.

allergic headache in whom the trial feeding of milk precipitated sharp head pain beginning two hours after ingestion. In the final graph a significant leukopenia was not measured, although this patient developed severe abdominal cramps three minutes after drinking milk, with excessive belching and nasal stuffiness at five minutes. She had an extreme degree of sensitivity to milk and complete avoidance has been necessary for relief of her perennial allergic rhinitis, bronchial asthma and gastro-intestinal symptoms. It is quite possible that a more significant leukopenia occurred in this instance prior to the twenty-minute blood observation. Obviously, in the event of such a clinical reaction one does not need to rely upon the blood findings to diagnose specific sensitivity. This type of blood response is of rare occurrence.

More commonly observed patterns of reaction associated with allergic

intolerance are listed in Figure 3. Graph 1 is from a patient subject to gastro-intestinal allergy and recurrent urticaria, who developed chilliness and lower abdominal pains forty minutes after the ingestion of beef. Spe-

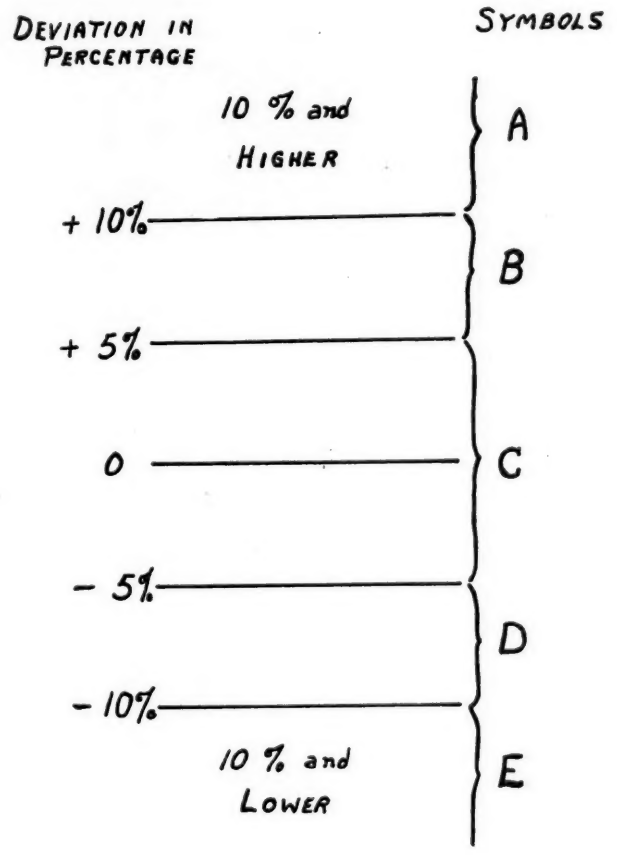

Fig. 4. A scheme for recording the results of individual food tests in terms of symbols representing the percentage variation of post-ingestive total leukocyte counts from the pre-ingestion level.

cific sensitivity was confirmed by continuing its use in the diet with the precipitation of acute abdominal cramps and diarrhea. Graph 2 is from a case of gastro-intestinal allergy with pronounced allergic fatigue, who developed chills at thirty minutes and a headache at fifty minutes following the ingestion of lettuce. Headache with residual fatigue persisted the following morning in association with several liquid stools. The third graph is from a child with infantile eczema, who developed an acute flare of dermatitis between eight and ten hours after test feeding with eggs.

The last graph is from a student with a diagnosis of giant urticaria, who developed an acute attack of hives four hours after the test. Diet trial has proved the specific diagnosis in each of these illustrative cases.

			Symptoms					Symptoms					Symptoms					Symptoms					Symptoms		Totals	
			−	+				−	+				−	+				−	+				−	+	−	+
A	A	A	36		A	B	A	4		A	C	A	4		A	D	A	1		A	E	A		1	45	1
B	A	A	8		B	B	A	4		B	C	A			B	D	A			B	E	A			12	
C	A	A	9	1	C	B	A	4		C	C	A	5		C	D	A			C	E	A		1	18	2
D	A	A	2		D	B	A			D	C	A	1		D	D	A			D	E	A			3	
E	A	A		1	E	B	A		1	E	C	A	1	3	E	D	A			E	E	A			1	5
A	A	B	4		A	B	B	1		A	C	B	1		A	D	B			A	E	B			6	
B	A	B	2		B	B	B	2		B	C	B	1		B	D	B			B	E	B			5	
C	A	B			C	B	B	2		C	C	B	7		C	D	B	1	1	C	E	B			10	1
D	A	B			D	B	B			D	C	B			D	D	B			D	E	B				
E	A	B			E	B	B			E	C	B		1	E	D	B			E	E	B				1
A	A	C			A	B	C	1		A	C	C			A	D	C			A	E	C	1	1	2	1
B	A	C	1		B	B	C	1	1	B	C	C	2		B	D	C			B	E	C			4	1
C	A	C	2		C	B	C		1	C	C	C	28	2	C	D	C	1	4	C	E	C	2	3	33	10
D	A	C			D	B	C	2		D	C	C	4		D	D	C	2	1	D	E	C		3	8	4
E	A	C	1	2	E	B	C			E	C	C	1	2	E	D	C	1	3	E	E	C	2	3	5	10
A	A	D		1	A	B	D	1		A	C	D			A	D	D			A	E	D			1	1
B	A	D			B	B	D			B	C	D		1	B	D	D	1		B	E	D			1	1
C	A	D	1		C	B	D	2		C	C	D	2	1	C	D	D	3	1	C	E	D	3	3	11	5
D	A	D			D	B	D			D	C	D		1	D	D	D	2		D	E	D		1	2	2
E	A	D			E	B	D			E	C	D			E	D	D	1	1	E	E	D	4	4	5	5
A	A	E			A	B	E	1		A	C	E	1		A	D	E			A	E	E		1	2	1
B	A	E			B	B	E			B	C	E		1	B	D	E			B	E	E	2		2	1
C	A	E		1	C	B	E			C	C	E			C	D	E		3	C	E	E	5	6	5	10
D	A	E			D	B	E			D	C	E	1		D	D	E			D	E	E	6	8	7	8
E	A	E			E	B	E			E	C	E	2	1	E	D	E	2		E	E	E	19	23	23	29
Totals			66	6				23	3				61	13				13	14				44	53	211	89

Fig. 5. The results of 300 consecutive individual food tests recorded in terms of symbols representing the percentage deviation of post-ingestive total leukocyte counts from the fasting levels and the presence or absence of associated symptoms.

A series of 300 consecutive individual food tests performed by three different technicians was subjected to a detailed analysis. As a matter of convenience in recording the results, each of the three post-ingestion leukocyte counts was classified as *A*, *B*, *C*, *D*, or *E*, according to the percentage deviation from the average of the two pre-ingestion total white cell counts. The symbols *A* and *E* indicate, respectively, an increase and decrease of 10 per cent or greater, *B* and *D*, an increase and decrease, respectively, of 5 per cent to 10 per cent, and *C*, an increase or decrease within 5 per cent of the basal leukocyte level. The basis of this classification is illustrated in Figure 4. It is apparent that the blood response of a given test may be represented as *AAA*, *EEE*, *BEC*, or any other combination of

the five letters. For instance, Graph 1 of Figure 2 would be designated as *EEE*, Graph 2 as *AEE*, Graph 3 as *CEA* and Graph 4 as *CAA*.

Figure 5 records the blood response of the 300 food tests classified according to these symbols and the presence or absence of symptoms occurring during or immediately following the procedure. Although all possible combinations of the five letters are listed, many combinations are not encountered and certain others are found with relative frequency. One should note the absence of symptoms associated with the *AAA* and related curves containing only the letters *A* and *B*, and the frequency of symptoms in the EEE and other combinations containing one or more *E*s.

The statistical significance of these data is more apparent when they are arranged in four-fold tables correlated by the chi-square technique. For instance, in comparing the curves where each post-ingestion count was 10 per cent or greater than the base line average (*AAA*) with those where each observation was 10 per cent or less (*EEE*) in respect to the presence or absence of symptoms, one obtains a chi-square of 16.08.

	Without Symptoms	With Symptoms	
AAA	36	0	36
EEE	19	23	42
	55	23	78

One may note that symptoms were not produced in any of the thirty-six AAA observations. Of the forty-two instances with an *EEE* response, nineteen were not associated with symptoms and twenty-three were accompanied by some evidence of clinical intolerance. If chi-square is greater than 3.84 the observed difference would arise by accidents of sampling less than five times in a hundred; if greater than 6.65 the observed findings occur accidentally less than once in a hundred times. The finding of 16.08 indicates that the association of the *EEE* type of curve and the presence of allergic symptoms would occur as a result of chance alone less than once in ten thousand times.

When four-fold tables are prepared comparing the blood responses containing one or more *E*'s with the curves which do not contain an *E* in respect to the presence or absence of precipitated symptoms, one obtains the highly significant chi-square of 78.62.

	Without Symptoms	With Symptoms	
E	56	73	129
Without E	155	16	171
	211	89	300

On the basis of this finding and the general experience that a 10 per cent or greater leukopenia in any of the three post-ingestive counts is associated with an incompatible clinical reaction, this degree of leukopenia has been established as indicating a positive test. According to this definition, that is, the presence of a leukopenia of 10 per cent or greater, there were 129

positive tests in the series of 300 consecutive observations performed in allergic patients. Symptoms were precipitated during or following completion of the tests in seventy-three of the 129, or 56.7 per cent.

Various symptoms may be produced, including those previously illustrated, a reproduction of the allergic complaint or any of the minor objective or subjective manifestations outlined in Rinkel's recent article. It is imperative that the test subject be maintained under close observation, as minor changes in the symptoms, behavior and appearance of the patient are of clinical importance. It might be added that all the manifestations enumerated by Rinkel have been observed over a period of six years during which one of us (T. G. R.) has had daily experience with trial feeding techniques. We concur in the importance of looking for certain special manifestations during the course of the individual food tests, such as unexplained fatigue, drowsiness, chilliness, sweating, flushing or abdominal distress; these symptoms occur commonly and obviously may be overlooked if one is not alert to their clinical significance. Frequently symptoms are not produced within the first hour after the initial feeding but are promptly precipitated by the second feeding. This conforms with well-recognized observations in handling food-sensitive allergic individuals, but may not be appreciated unless one has had the experience of following their cases with carefully recorded food and symptom diaries. Telltale symptoms are sometimes delayed several hours, as in some of the cases illustrated; this is particularly true with an accentuation or recurrence of urticaria, eczema or diarrhea.

It should be noted that symptoms were not observed in approximately 40 per cent of the positive tests, that is, in the presence of a leukopenia of 10 per cent or greater. For several months all instances of this type were checked by cumulative feeding of the suspected food. Under such circumstances the diagnostic validity of the post-ingestive leukopenia as defined was usually upheld. As a result of efforts to check clinically both the positive and negative tests as determined hematologically, we have been impressed with the relative accuracy of the blood observations in detecting clinically offending foods even though the test feeding was not followed by the precipitation or association of symptoms. As experience with the method increases, one learns to respect the presumptive evidence of sensitivity afforded by the presence of a leukopenia in the absence of symptoms. This is a valuable criterion of current specific sensitivity in instances where diagnosis is most difficult, that is, where foods are responsible for symptoms because of their latent or cumulative action.

Not infrequently, however, one finds associated symptoms in the presence of leukopenia between 5 and 10 per cent (*D*) and occasionally when the decrease in leukocytes is less than 5 per cent (*C*). It must be pointed out that the symptoms are both objective and subjective and that particularly the latter may not necessarily be the result of an allergic reaction. From experience one learns that certain subjective symptoms usually indicate

specific incompatibility and only those subjective manifestations commonly recurring and found to be of clinical importance are judged to be of significance. As previously mentioned, these reactive symptoms have been fully described in Rinkel's recent presentation. The factor of suggestion in relation to symptoms is controlled so far as possible in that the patient is given no indication of the results of the blood counts during the tests or for the remainder of the same day. It should also be stated that the majority of the tests were performed with the major allergens (wheat, corn, milk and eggs) for, as a rule in undiagnosed cases, specific sensitivity to these foods is not suspected due to the fact that they most commonly cause masked or cumulative types of reactions.

When the curves including an *E* in any of the three observations and a *D* in either the forty- or sixty-minute blood counts are compared with others one obtains a chi-square of 89.27.

	Without Symptoms	With Symptoms	
E or D 40 or 60	73	84	157
Others	138	5	143
	211	89	300

Out of the 300 tests one is left with only five observations where significant symptoms were observed in the presence of a relatively flat type of blood response. Indeterminate hematologic findings occur between 5 and 10 per cent of tests; they may or may not be associated with evidence of clinical sensitivity and one must resort to cumulative test feeding after symptoms have been relieved to prove or disprove sensitivity in such instances.

In order to gain further information in this type of reaction, for a period of several months we performed total leukocyte counts at twenty-minute intervals for an hour after the second feeding, in addition to the standard routine. We encountered only an occasional instance of unquestioned clinical sensitivity where an absence of a 10 per cent leukopenia during the first period was followed by a diagnostic diminution of leukocytes after the second feeding. From this experience and the observation that telltale symptoms are so commonly produced immediately after the second feeding, we concluded that it is not necessary as a routine to perform additional leukocyte counts providing the patient remains under clinical observation for at least one-half hour after the second feeding.

The most significant observation to be drawn from these data is the fact that a trajectory type of post-ingestive leukocytosis has never been observed in the presence of allergic intolerance, as shown by the production of symptoms during or following the test or as a result of cumulative feeding immediately following this diagnostic procedure. This statement, again confirming Rinkel's observations, is based not only on the 300 tests tabulated in this survey, but also on an additional series of 1,500 other individual food tests. Under the terms of this procedure it may be said with safety that the presence of a trajectory type of post-ingestive

leukocytosis indicates specific allergic tolerance *at the time of the test.* The temporal aspect of this statement must be emphasized, for therein lies the greatest advantage of the individual food test, that is, its ability in detect-

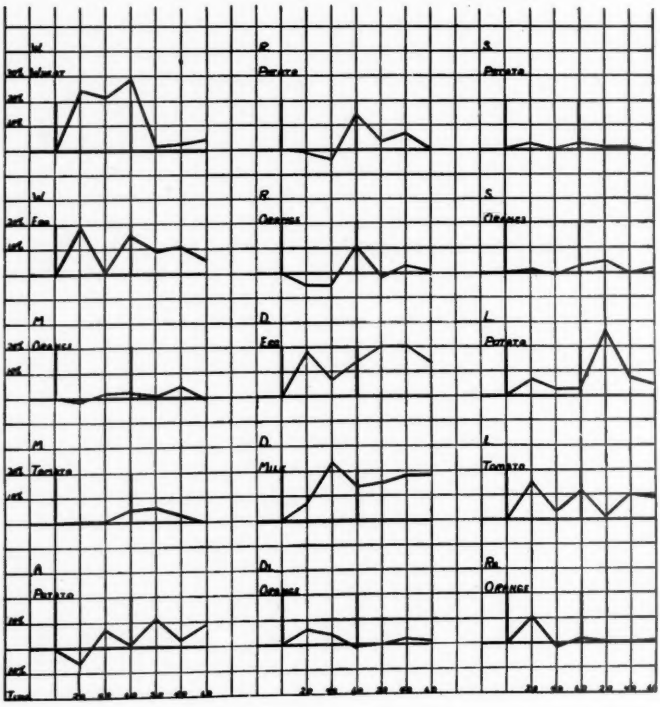

Fig. 6. The results of fifteen individual food tests in nine normal non-allergic individuals with total leukocyte observations at twenty-minute intervals after each of two feedings.

ing current tolerance or intolerance. The well-known clinical observations that tolerance to a specific allergen may be acquired as a result of avoidance or that a spread of sensitivity to a previously tolerated food may occur as the result of cumulative feeding, have been repeatedly observed and measured by this test technique.

It is inconceivable that the association of symptoms with the type of blood response as illustrated in these data could possibly occur by chance. The frequency of symptoms occurring in association with the incompatible blood response as judged by the definition of a leukopenia of 10 per cent or greater, and the absence of symptoms in the presence of a trajectory type of plotted curve, attest to the accuracy of this diagnostic method.

The major emphasis in the interpretation of the individual food test is placed on the symptom response, which is accentuated by the specific prep-

aration of the patient and by the administration of two doses of the test food. The presence of diagnostic symptoms is usually supported by the concurrent finding of a post-ingestive leukopenia. With symptoms of questionable significance the presence of a postprandial leukopenia is additional evidence in support of specific sensitivity. In the absence of precipitated or accentuated symptoms in association with test feeding one may assign diagnostic significance to various changes in the total leukocyte counts. The presence of a trajectory type of postprandial leukocytosis indicates current allergic tolerance for the tested food. A post-ingestive leukopenia of 10 per cent or greater in any one or several of the determinations is presumptive evidence of specific sensitivity. For these reasons, it is desirable to perform total leukocyte counts in association with experimental ingestion of the suspected food.

The identical technique with serial counts for sixty minutes after both the first and second feedings was carried out fifteen times in nine normal non-allergic individuals, each prepared by four days of specific avoidance prior to the test. The plotted results are shown in Figure 6. It should be observed that in no instance in this series did the total leukocyte count diminish more than 5 per cent from the basal pre-ingestion average. There were no symptoms even slightly suggestive of allergic intolerance following test feeding in these cases.*

DISCUSSION

Although Vaughan's[16,17,18] subsequent publications and the early reports of Rinkel[10], Zeller[19], Rinkel and Gay[12] and Gay[2], all in 1936 confirmed the value of the leukopenic index, Loveless, Dorfman and Downing[3], and Brown and Wadsworth[1] published highly critical articles in 1938. Before discussing the objections of the latter authors, it should be emphasized that the current technique used by Rinkel and employed in the present study (except for minor variations mentioned) differs materially from earlier procedures in that the patient is tested to a food previously eaten regularly, then completely avoided for four days and tested on the fifth. This preparation of the patient accentuates both the clinical manifestations and the hematologic variations. Furthermore, the use of the individual food test as advocated by Rinkel and by us applies to the specific diagnosis of cases of unknown food sensitivity. As a general rule, allergic patients seek aid when having troublesome symptoms. Under such circumstances one may generally expect a higher incidence of reactive symptoms and a greater liability of the blood response than during periods of relative allergic balance.

Specific objections to procedures of this type have dealt principally with the question of the accuracy of total leukocyte determinations, with an apparent indifference to the wealth of clinical evidence of sensitivity which

*Illlustrative of the difficulty of selecting "normals" in this respect is the fact that Case R has developed unquestioned allergic reactions since this manuscript was submitted for publication. Allergic headaches have been experimentally induced on repeated occasions following ingestion of peanuts, beans and cauliflower.

is afforded by the observation of patients during the course of and immediately following individual eating tests. The high incidence of reactive symptoms associated with the trial feeding of foods, previously included in the diet but avoided for four days prior to the test, warrants the general use of this procedure. Quite aside from the controversy over the accuracy of the technique of leukocyte counting, the test feeding of specific foods is decidedly worth while from the standpoint of clinical observations afforded, whether or not serial leukocyte determinations are performed.

Loveless, Dorfman and Downing based their statistical analysis of the old leukopenic index on feeding tests with a group of non-allergic and a group of allergic individuals with known clinical food reactions. The blood response in the normals (their Group I) may be questioned, as they employed a test meal of wheat, milk and eggs instead of testing with individual foods. By using cases of known clinical sensitivity one might reasonably assume, at least from our experience, that these patients had been either avoiding the specific food for extended periods prior to the test or had been eating the questioned food in amounts not sufficient to produce symptoms and, thereby, were in a state of relative tolerance at the time of experimental testing. One certainly obtains the impression from the report of Loveless and coworkers that their test subjects did not submit themselves for relief of acute or chronic allergic manifestations at the time of the experimental observations. This is a very important point, and serves to emphasize the fact that their cases were selected on a different basis from that of the original or the current advocates of diagnostic feeding techniques.

The same criticism regarding the selection of allergic patients may be made in reference to the article of Brown and Wadsworth.

We observed similar difficulties when attempting to evaluate individual food tests in selected cases of known food sensitivity. Convincing clinical and hematologic evidence was not obtained until we started to study cases of uncontrolled allergy and adopted the routine of testing with foods previously eaten regularly but avoided for a short constant period prior to trial feeding.

The correct interpretation of the individual food test requires a working knowledge of the various phases of tolerance through which the food sensitive patient passes in respect to the length of specific avoidance. This knowledge is gained as a result of the detailed experience of handling food sensitive individuals by means other than the common but unfortunate practice of interpretating literally skin tests with food allergens. The findings of the individual food test are reproducible and the results are relatively easy to interpret if the factors of tolerance and the length of avoidance are constant as, for instance, in the observations of the present series.

The interpretation of food tests in cases of known sensitivity is fraught with hazard unless these variable factors are considered. A heterogenous

group in this respect is not fit material for statistical analysis and from such a group conclusions concerning the reliability of the technique should not be drawn. It is imperative, therefore, that critics of techniques of this type attempt to use them in the sense employed by their advocates, namely, as diagnostic aids in studying food allergy instead of using this method to check cases of known sensitivity which, at the time, may be in various phases of clinical tolerance or intolerance.

It is by no means suggested that this is the only technique by which food allergy may be diagnosed. Basic elimination diets of the type recommended by Rowe[13] cannot be displaced, and there is no desire to do so. The chief practical value of the individual food test is the ability to detect current specific tolerance or intolerance to the foods which most commonly produce cumulative or latent reactions. The technique may be used to advantage in supplementing the basic type of elimination diets, either by testing of major suspects prior to the prescription of a comprehensive elimination plan or by checking questionable food following such a procedure.

Perhaps the greatest value of the individual food test pertains to the instruction of the patient and the physician. The clearcut demonstration of symptoms which so frequently occur under the circumstances of the test tends to convince the skeptical patient and insures a greater degree of co-operation in following a restricted diet than might otherwise be the case. Its routine use demonstrates many of the basic principles of food allergy dependent upon variations in specific tolerance, which otherwise are observed with greater difficulty.

SUMMARY

From a detailed study of 300 consecutive individual food tests performed in undiagnosed allergic individuals, we are able to confirm Rinkel's claim that the individual food test is a helpful and accurate aid in the current diagnosis of specific food sensitivity. Further experience with this method in the routine diagnosis of food allergy supports this conclusion.

It is to be emphasized that cases of undiagnosed clinical allergy were studied and that the specific food in question previously included in the diet, was eliminated for a period of four days prior to trial feeding. Testing patients in this phase of clinical intolerance materially accentuates the evidence of sensitivity as judged by the more constant production of symptoms in association with a diagnostic post-ingestive leukopenia.

Under the circumstances of this test there is a high degree of correlation between the presence of a post-ingestive leukopenia of 10 per cent or greater, and the production of symptoms of intolerance associated with test feeding or with evidence of specific sensitivity as a result of cumulative feeding. Symptoms suggestive of allergic intolerance occasionally occur with lesser degrees of leukopenia, but have not been observed in the presence of

a trajectory type of postprandial leukocytosis as a result of performing over 1,500 individual food tests.

* * *

We are indebted to Dr. Frederic T. Jung, Associate Professor of Physiology, Northwestern University Medical School, for helpful suggestions regarding the mathematical treatment of data.

REFERENCES

1. Brown, E. A., and Wadsworth, G. P.: Leukopenic index. J. Allergy, 9:345, 1938.
2. Gay, L. P.: Gastro-intestinal allergy; the leukopenic index as a method of specific diagnosis of allergens causing peptic ulcer. J.A.M.A., 106:969, 1936.
3. Loveless, M., Dorfman, R., and Downing, L.: Statistical evaluation of the leukopenic index. J. Allergy, 9:321, 1938.
4. Randolph, T. G.: Blood studies in allergy. I. The direct counting chamber determination of eosinophils by propylene glycol stains. J. Allergy, 15:89, 1944.
5. Randolph, T. G.: Blood studies in allergy. IV. Variations in eosinophils following test feeding of foods. J. Allergy, (in press).
6. Randolph, T. G.: Charts for determining the percentage variation of total leukocyte counts. Am. J. Clin. Path, (in press).
7. Randolph, T. G., and Rawling, F. F. A.: Blood studies in allergy. III. Cellular reactions in sulfonamide sensitivity. J. Allergy, 16:17, 1945.
8. Randolph, T. G., and Stanton, C. L.: A comparison of the differential counts from the stained film and counting chamber using a propylene glycol aqueous stain. Am. J. Clin. Path., 15:17, 1945.
9. Rinkel, H. J.: Gastro-intestinal allergy. II. Concerning the mimicry of the peptic ulcer syndrome by the symptoms of food allergy. Southern M. J., 27:630, 1934.
10. Rinkel, H. J.: The leukopenic index in allergic diseases. J. Allergy, 7:356, 1936.
11. Rinkel. H. J.: Food allergy. II. The technique and clinical application of individual food tests. Ann. Allergy, 2:504, 1944.
12. Rinkel, H. J., and Gay, L. P.: The leukopenic index, technique and interpretation. J. Missouri M. A., 33:182, 1936.
13. Rowe, A. H.: Elimination Diets and the Patient's Allergies. A Handbook of Allergy. 2nd Ed. Philadelphia: Lea & Febiger, 1944.
14. Squier, T. L., and Madison, F. W.: The hematologic response in food allergy, eosinophilia in the leukopenic index. J. Allergy, 8:250, 1937.
15. Vaughan, W. T.: Food allergens. III. The leukopenic index, preliminary report. J. Allergy, 5:601, 1934.
16. Vaughan, W. T.: Further studies on the leukopenic index in food allergy. J. Allergy, 6:78, 1934.
17. Vaughan, W. T.: The leukopenic index as a diagnostic method in the study of food allergy. J. Lab. & Clin. Med., 21:12, 1936.
18. Vaughan, W. T.: Practice of Allergy. Page 228. St. Louis: C. V. Mosby Co., 1939.
19. Zeller, M.: The leukopenic index in intractable asthma. Illinois M. J., 69:54, 1936.

THE IMMUNOCHEMISTRY OF ALLERGENS. VIII. Precipitin Formation and Passive Transfer Reactions with Allergenic Proteins from Cottonseed and Castor Beans. Colson, E. J., et al.; J. Immunology, 52, 259, 1946.

The authors conclude from extensive experimental data that the allergenic proteic-polysaccharidic fractions from cottonseed and castor beans were precipitinogenic but that these fractions were less effective than ovalbumin in stimulating precipitin formation. Passive transfers are more sensitive for detecting serum antibodies than the precipitin method.

ETHYLENE DISULPHONATE IN CHRONIC ASTHMA

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NEW theories concerning allergic diseases were presented in 1939 and 1940 by Evans, Bodman and Maisin.[5] They stated that the primary cause of allergy is a departure from normal in the chemistry of cellular metabolism involving the absence of certain catalysts of co-enzyme activity. An adequate supply of catalysts, making good the deficiency, would resolve the allergic state. They believed that the chemical energy produced and distributed by the metabolic activity of the living cell was essential for its normal function. Abnormalities of such metabolism involving an alteration in oxidation-reduction within the cells were believed responsible for the production of the allergic state. The changes could be due to shock, whether injective, traumatic or emotional, generally occurring in a person rendered susceptible by inherited tendency. The site and specific nature of cells affected would alone determine the type of allergy exhibited.

The fundamental need in the treatment of allergic state would be the recovery of the normal oxidation chain involved in the production and normal distribution of cell energy. This appeared to depend on the restitution of a normal carrier catalyst cycle by the provision of a substance (an oxidation catalyst) the absence of which is the direct result of the kind of trauma already referred to. A search by Evans and his co-workers for the substance led to the discovery of ethylene disulphonate, prepared by Endocrines-Spicer Ltd., of Watford, England. The drug was dissolved in triple-distilled water in pyrex glass containers and quickly sealed in ampoules, since the solution was considered to be highly unstable and rapidly oxidized in the presence of air, certain chemical substances, oil or grease, Recent observations reveal that the chemical will not disintegrate easily (Fig. 1).

The first laboratory investigation, which was reported, involved the use of thirty guinea pigs all of which were sensitized by two intraperitoneal injections (eight days apart) of Mercks crystalline egg albumin in doses of 0.1 gram. The animals were divided into two groups, namely A and B. Group A received 1 c.c. of the solution of ethylene disulphonate and Group B acted as a control. Three hours later all animals were given a shocking dose of 0.8 gram of egg albumin. There were no deaths in Group A, but in Group B one-third of the animals died. The same protection was still present if the shock dose was administered twenty-four, forty-eight or seventy-two hours after the drug was injected.

Another animal experiment was conducted. Group A now was given

From the Minneapolis General Hospital and the Medical School of the University of Minnesota.
*Deceased.

three doses of 1 c.c. of the ethylene disulphonate solution at eight-day intervals. Two months after the last injection, the animals of both groups received a shocking dose of 0.8 gram of egg albumin with the result that 33 per cent of Group A died and 95 per cent of Group B.

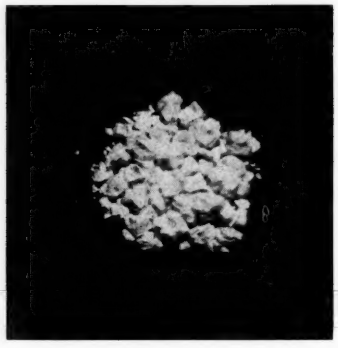

Fig. 1. A small supply of ethylene disulphonate. Before the material is dissolved in water, it appears to be quite stable.

Smith[11] of this country made a study with twenty guinea pigs. He sensitized the animals with egg albumin as described by Evans, Bodman and Maisin. Twenty-eight days following sensitization, one-half of the guinea pigs were injected intraperitoneally with 1 c.c. of the solution of ethylene disulphonate and three hours later all the animals were given a shocking dose of egg albumin. Two of the treated animals succumbed while none of the controls lived.

Fisk, Small and Foord[7] using a large number of guinea pigs and the same procedures had a mortality rate of 60.61 per cent among thirty-three animals receiving ethylene disulphonate, 67.74 per cent among thirty-one guinea pigs which were given distilled water and 72 per cent among animals untreated and acting as controls. The authors concluded that the differences were within the limit of standard error and the odds were due to chance. They could not confirm the work of Evans and his associates, nor that of Smith.

The English investigators also carried out some clinical studies. After preliminary experimentation they decided that the best results would be obtained if the individuals receiving ethylene disulphonate were given a special routine of preparation. Each patient was required to drink over a period of five minutes one quart of warm or cold water containing two level teaspoons of salt one-half hour before breakfast for three consecutive mornings. Bilisolin (Endocrines-Spicer Ltd.) was recommended for five days or until free bile appeared in the stool. Drugs such as morphine, barbiturates, alcohol, tobacco and aspirin were withheld for one

TABLE I. SEVENTY-ONE CASES TREATED BY EVANS, BODMAN AND MAISIN

No. Injections Ethylene Disulphonate	Complete Control of Allergic Symptoms		Partial Control of Allergic Symptoms		No Change	
	No. Cases	Per cent	No. Cases	Per cent	No. Cases	Per cent
One	7	9	8	11	2	3
Two	8	11	17	24	0	0
Three	4	6	23	33	2	3
Total	19	26	48	68	4	6

week before and three weeks after an injection of the ethylene disulphonate solution. The diet of the allergic patients was made high in vitamins B_1, B_2, and C. No meat was permitted for one week prior to an injection and three weeks thereafter.

The technique of administration of the solution of ethylene disulphonate was carefully controlled by Evans and his co-workers. The skin was cleaned without using a disinfectant. The drug was quickly drawn from the 2 c.c. ampoule into a syringe, a needle attached and an injection made rapidly into the triceps muscle.

This form of therapy gave favorable results in 94 per cent of the patients as shown in Table I.

Smith[10] carried on the clinical work. In 1942 he reported upon a group of thirty-three allergic adults including twenty-five individuals suffering from asthma, six with asthma who exhibited urticaria and eczema, one patient with migraine, and one case of "skin manifestation." Successful results were obtained in 82 per cent of the patients and another 8 per cent were greatly relieved.

Wasson[12] studied forty children with asthma, eczema, hay fever, urticaria or any combination of these conditions and presented the results in 1943. The author gave twenty patients the ethylene disulphonate solution, the remainder acting as controls. Completely relieved were eleven children receiving the drug, while among the controls six cases received satisfactory results from other forms of therapy.

Bartlett [2,3] reviewed his cases and published the work in 1944. He had excellent results among 247 children and fairly good relief among 528 adults, which led him to conclude that the treatment of the allergic state with ethylene disulphonate is a decided advance in therapy. This conclusion was given further support by the report of Feder and Tribble.[6] They also had favorable results when using the drug and felt it was a new hope for the allergic.

Recently, however, less favorable reports have appeared. Archibald[1] observed forty-five children over a fairly long period of time and in his publication of 1945 he states that the use of ethylene disulphonate in-

dicates a non-specific form of treatment which although occasionally very beneficial in the allergic individual is disappointing in the long run. Kurland and Bubert[8] made a thorough investigation in a small group of adults. They followed as closely as possible the recommendations of

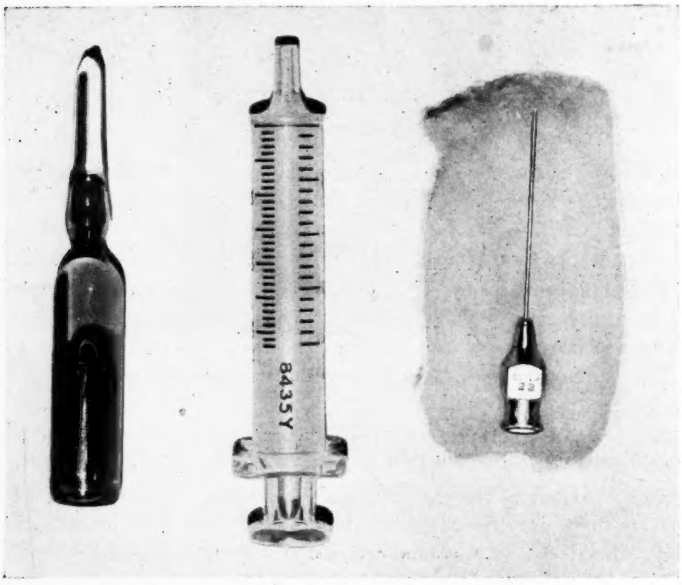

Fig. 2. One 2 c.c. size ampoule of ethylene disulphonate (Allergosil Brand) in a dilution of 10-15 in triple-distilled water with the specially cleaned syringe and needle furnished by the manufacturer.

Evans, Bodman and Maisin and treated twelve cases of asthma with the drug. Observations were made over an average of seventeen weeks and it was found that ten patients gave no response and two showed some improvement. As a result these investigators concluded in their preliminary report of 1945 that the claims for ethylene disulphonate are completely excessive.

The present study of the therapeutic value of ethylene disulphonate was made in a selected group of fifteen cases with chronic asthma. All the individuals were receiving treatment based on complete diagnostic procedures. Offending foods were eliminated from the diet, irritating inhalants were avoided, and in some instances foci of infection were removed. Little improvement occurred and the patients were admitted to the hospital where there was no change in symptoms.

Each case was prepared for the administration of the ethylene disulphonate as recommended by the manufacturer. An adequate diet of normal

TABLE II. TEN CASES OF CHRONIC ASTHMA RECEIVING ETHYLENE DISULFONATE

Case No.	Sex	Age	Yrs. of Asthma	Injection of Ethylene Disulphonate	Results
1-EC	F	26	4½	3 injections one day apart and one 6 weeks later	Poor
2-RS	M	70	60	2 injections 2 weeks apart and one 6 weeks later	Fair
3-JW	M	51	9	2 injections 2 weeks apart and one 6 weeks later	Poor
4-GW	F	26	7	2 injections 2 weeks apart and one 6 weeks later	Poor
5-VV	M	68	7	2 injections 2 weeks apart and one 9 weeks later	Fair
6-EH	F	31	13	2 injections 2 weeks apart and one 6 weeks later	Poor
7-WM	M	56	10	2 injections 2 weeks apart and one 9 weeks later	Poor
11-JR	M	37	30	2 injections 2 weeks apart and one 6 weeks later	Poor
14-AN	F	54	20	2 injections 2 weeks apart	Poor
15-CP	F	42	38	2 injections 2 weeks apart	Good

TABLE III. FIVE CASES OF CHRONIC ASTHMA RECEIVING TRIPLE-DISTILLED WATER

Case No.	Sex	Age	Yrs. of Asthma	Injection of Ethylene Disulphonate	Results
8-JH	M	66	35	2 injections 3 weeks apart and one 9 weeks later	Good
9-JC	M	52	26	2 injections 2 weeks apart	Fair
10-FS	M	63	5	2 injections 2 weeks apart	Poor
12-HS	M	76	12	2 injections 2 weeks apart	Fair
13-JO	F	30	9	2 injections 2 weeks apart and one 6 weeks later	Poor

energy value was provided. No meat was permitted for one week before and three weeks after the injection of the drug. Sugar was reduced in the diet by avoiding the use of refined or raw sugar in foods or drinks, and this loss in calories was replaced by giving more whole cereal grains. Vitamins B_1, B_2, and C were kept at a high level.

The bowel was washed through by causing each patient to drink one quart of cold or warm water containing two level teaspoonfuls of common salt, half an hour before rising. The whole quart was drunk within five minutes. The procedure was carried out for three consecutive mornings and then once weekly.

Alcohol, aspirin, barbiturates, sulfonamides, opium derivatives, and tobacco were omitted during the entire period of the investigation.

After a week of preparation, the first injection of one 2-c.c. ampoule of ethylene disulphonate (Allergosil Brand)* in a dilution of 1.10-15 in triple-distilled water was made in ten cases, and of sterile triple-distilled water in five cases which acted as controls. The manufacturer's technique of injection was followed in all patients and is here presented (Fig. 2).

"The skin is cleaned by rubbing with sterile wool. No disinfectant may be used. The syringe is then assembled and the neck of the ampoule removed, the contents being drawn into the syringe. Then (and not until then) the needle is placed in position. The injection is then made deep into the triceps, or deltoid, muscle.

*Obtained from Spicer-Gerhart Company of Pasadena, California, by the Food and Drug Administration, Federal Security Agency, Washington, D. C., and sent by registered mail to the authors who used the drug before the expiration date on each package.

The object should be to introduce the material from the ampoule to the muscle as rapidly as possible and with as little exposure as possible to air and metal. After the injection, watch until a natural seal of the puncture has taken place. No applications whatever are to be used except pressure with sterile, dry cotton wool."

Further injections of the solution of ethylene disulphonate or the triple-distilled water depended upon the progress of each case. Hospitalization afforded an opportunity to watch all patients carefully. Records of all complaints were made and physical examinations were performed frequently.

The results are summarized in Tables II and III.

All the patients receiving the ethylene disulphonate solution experienced muscle fibrillation and some pain after the injections. The first patient was made worse by the drug while the second felt better in spite of little change in physical findings. However, after three months, the asthma returned with frequent severe attacks. The improvement in the third case continued for ten days after which bronchopneumonia developed and the asthma was made worse. The fourth, sixth and seventh cases were complete failures. The fifth patient had less complaints and there was improvement on physical examination. Case eleven revealed marked muscle fibrillation and much pain. He did poorly. The next patient was relieved for only one week, but the last patient had a more lasting improvement. She was very enthusiastic over the treatment for many months.

There was also muscle fibrillation and pain in association with the injection of triple-distilled water. The first case of this group had a satisfactory response. After a second injection of the distilled water he had only one attack of asthma each week instead of the usual daily one. Two more patients, namely, nine and twelve, showed improvement, with patient nine expressing definite relief while the other patient revealed physical findings of less asthma. The remaining two patients did not respond; in fact, the last patient was made worse and objected to the triple-distilled water injections.

The chronic asthmatic patients of this study received the best of care. All known methods of diagnosis and therapy were employed and in spite of all this work, the symptoms continued. Ethylene disulphonate was considered on account of early favorable reports,[5,11] Ten patients received the drug and five others were given triple-distilled water. All rules and regulations requested by the manufacturer of the ethylene disulphonate solution were followed. This was possible because of the fact that the patients were in the hospital and could be watched continuously.

The results from the use of the drug were far from satisfactory. The small series of patients chosen gave an opportunity to study the effect of ethylene disulphonate closely and under these circumstances only a few

of the cases receiving the drug showed a good response. The same picture was revealed by the patients receiving plain distilled water, a form of therapy first tried several decades ago.[9]

The clinical effects of ethylene disulphonate and triple-distilled water are similar. Any favorable action is not specific. The possibility of a psychological reason for the results may be considered but in the present investigation was not confirmed. The most neurotic patients did not respond satisfactorily to the drug or the water therapy. There still may be a physiological stimulation but this is not necessarily due to ethylene disulphonate.[4]

CONCLUSIONS

An intensive study of the use of a solution of ethylene disulphonate (Allergosil Brand) in a small group of chronic asthmatic hospital patients showed that the drug is of little value.

The results were no better than those obtained from the administration of triple-distilled water.

If the few favorable responses from both forms of treatment are not based on a psychological background, then there may be other reasons, the thought of which warrants further investigations of the whole field of non-specific therapy in allergic diseases.

REFERENCES

1. Archibald, H. C.: Ethylene disulphonate and sterile distilled water controls in the treatment of children's allergies. Arch. Pediat., 62:219-222, 1945.
2. Bartlett, C. L.: Treatment of the allergic state in children with ethylene disulphonate. Arch. Pediat., 61:311-316, 1944.
3. Bartlett, C. L.: Treatment of the allergic state with ethylene disulphonate. M. Rec., 157:477, 1944.
4. Current Comment: Ethylene disulphonate launched as a cure for asthma. J.A.M.A., 120:842, 1942.
5. Evans, G., Bodman, J., and Maison, J. H.: The chemical control of allergy. Med. Press and Circular, 203: No. 5273 and 5274, (May) 1939 and (June) 1940.
6. Feder, J. M., and Tribble, E.: New hope for the allergic; use of ethylene disulphonate. Southern Med. & Surg., 106:52-53, 1944.
7. Fisk, R. T., Small, W. S., and Foord, A. G.: Experimental use of ethylene disulphonate in the prevention of anaphylaxis in guinea pigs. J. Allergy, 15: 14-17, 1944.
8. Kurland, L. T., and Bubert, H. M.: Ethylene disulfonate in bronchial asthma. Bull. School Med., Univ. Maryland, 30:46-50, 1945.
9. Schatz, E.: Details in the treatment of hay fever, asthma and other manifestations of allergy. Am. J. M. Sc., 166:645, 1923.
10. Smith, N. M.: The basic treatment of allergic manifestations. Clin. Med., 49:324-327, 1942.
11. Smith, N. M.: Chemical control of allergy. Mississippi Valley M. J., 65:20-23, 1943.
12. Wasson, V. P.: Ethylene disulphonate in the treatment of allergic children. Arch. Pediat., 60:511-517, 1943.

PENICILLIN DERMATITIS BASED ON TUBERCULIN-TYPE SENSITIVITY

Report of a Case with Remarks on Experimental Sensitization to Penicillin

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REPORTS of allergic sensitization from penicillin are increasing. The following case of local sensitization through external contact with penicillin is reported because it appears based on tuberculin-type sensitivity.

CASE REPORT

The patient, a nurse twenty-six years of age, presented herself September 11, 1945, on account of a vesicular dermatitis involving several fingers of both hands. This eruption originated about six months ago, shortly after penicillin treatment was introduced at the hospital where the nurse worked. The dermatitis began with little blisters on several fingers. The patient remembers that she spilled some of the solution over her fingers. The eruption cleared up on several occasions when the nurse was off duty, and also at the hospital when she kept away from penicillin.

On examination a slight vesicular eruption on several fingers of both hands was noted. The results of the general examination were irrelevant. Routine patch tests with common contacts including soaps were negative. Intradermal tests with various mycotic and bacterial antigens gave a 2+ reaction to trichophytin, 3+ to oidiomycin, and minor reactions to staphylococcus and streptococcus; the latter not different from those usually elicited in adults. The patient had suffered previously from a dermatophytosis of the feet which accounted for the positive trichophytin reaction. Intradermal tests with commercial mold antigens of penicillium notatum, penicillium glaucum and aspergillus were negative.

TESTS WITH PENICILLIN

Intradermal tests with penicillin regularly produced a tuberculin-type delayed reaction. Tests were carried out and repeated with sodium penicillin (Lilly), and calcium penicillin (Winthrop); 250 to 1,000 units contained in 0.05 or 0.1 c.c. of normal saline solution were used. An intradermal test with crystalline sodium penicillin "G", containing 500 units (0.3 mgm.) gave the same positive result.

There was no true urticarial reaction, although a small wheal appeared at all sites immediately; but this was not different from the wheal occurring in non-sensitive controls. However, about ten to twelve hours later a delayed reaction appeared, with a maximum of about twenty-four to forty-eight hours, presenting itself as a tuberculin-type infiltrated itching lesion

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**From the Monroe Hospital, Monroe, Michigan, and the Department of Dermatology, Wayne University, Detroit.

of from 1.2 to 1.8 cm. in diameter (Fig. 1, right side. Left side shows negative controls on the arm of a different patient).

The histologic picture of such a reaction examined twenty-four hours

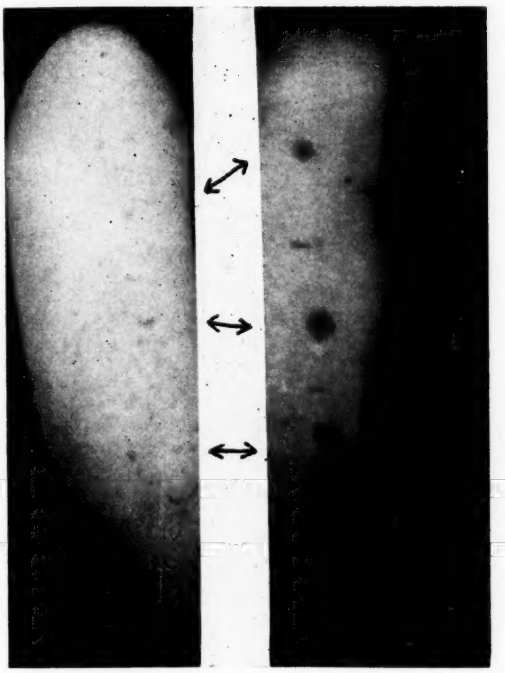

Fig. 1. Tuberculin-type reaction to different commercial penicillins after forty-eight hours (right side of picture). Note completely negative controls on the arm of a normal volunteer (left side of picture; arrows point in their direction).

after the injection of the penicillin was that of a localized cutaneous inflammation (Fig. 2), typical of a "tuberculin type" response:

"The epidermis is practically normal. The corium shows edema and diffuse increase of fixed connective tissue cells with swollen nuclei. The blood vessels are filled with polymorphonuclear cells and surrounded with dense sheaths of lymphocytes. The center of the pathologic reaction is in the mid-corium. No eosinophiles are found. Mast cells are present in average numbers."

This tuberculin-type reaction persisted for some time. The infiltration subsided and eventually turned into a superficial eczema-like lesion which presented itself three weeks later as a mild dermatitis. The biopsy at that time presented the picture of a subsiding mild dermatitis:

"The epidermis is acanthotic, about twice the normal thickness and slightly ede-

matous. The edema is mostly intracellular. Keratohyalin and keratin layers are normal except in one relatively small area which is parakeratotic with loss of the granular layer. However, there are several areas where a parakeratotic scale

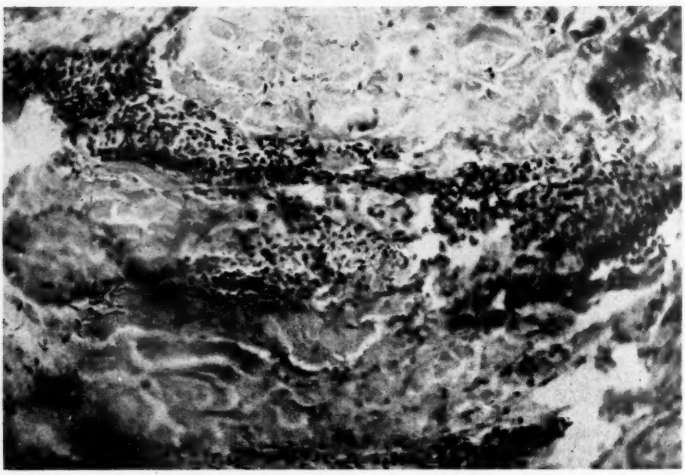

Fig. 2. Microscopic appearance of tuberculin-type reaction as presented in Figure 1. Note edema of corium and lymphocytic, largely perivascular infiltrate.

is superimposed on the normal horny layer. There is barely any cutaneous edema, but the subpapillary blood vessels have thickened walls and show mild perivascular sheaths of round cells."

Patch tests—Numerous patch tests with penicillin performed on normal skin of the arms and legs of the patient, in solution as well as with dry commercial penicillin powder, were negative. Patch tests on fingers that had not been affected previously were also negative. However, when a patch test with a few drops of a penicillin solution containing 5,000 Oxford units in 1 c.c. was performed on the patient's fingers at a site that previously had shown an eruption, itching was noted within three hours. At that time a localized eruption consisting of small pinpoint to pinhead sized vesicles was noticed. The vesicles increased somewhat in size. After twenty-four hours a picture of "dysidrosis," an eruption of clear vesicles, was present (Fig. 3).

A biopsy of this vesicular eruption taken twenty-four hours after the application of the penicillin solution showed the typical picture of a "dysidrosis" type of dermatitis)Fig. 4, *A* and *B*) :

"The typically thick epidermis of the finger shows spotty edema, spongiosis and vesiculation in different levels. Upon closer scrutiny one finds that most of the vesicles and areas of spongiosis are connected with ducts from sweat glands.

There is considerable transmigration of leukocytes which partly disrupts the epidermal structure. The papillae and the subpapillary layer are highly edematous and show lymphocytic infiltration around the widened blood vessels which contain polymorphonuclear leukocytes. Eosinophiles are absent."*

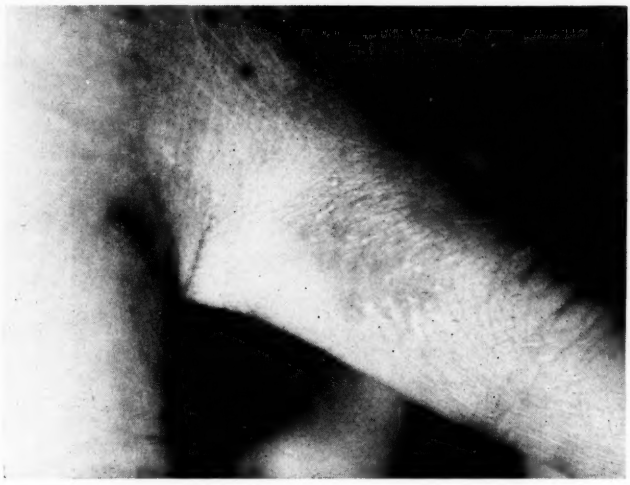

Fig. 3. Vesicular "dysidrotic" eruption of finger, twenty-four hours after application of commercial penicillin. A few drops of a solution containing 5000 units per 1 c.c. were applied for three hours.

A patch test with penicillin at the site of a former positive intradermal test produced redness after eighteen hours, but no blisters and no pruritus.

PASSIVE TRANSFER

Passive transfer of the sensitivity was attempted on four volunteers. The results were completely negative in three instances. In the fourth instance a slight redness about 5 mm. in diameter was noticeable after twenty-four and forty-eight hours at both sites tested. Although the control sites did not react, the evidence does not seem great enough to be definitely considered a positive passive transfer.

EXPERIMENTAL SENSITIZATION TO PENICILLIN

Of the four volunteers that were used for controls and passive transfer, two became sensitized to commercial penicillin. Only one of them was available for further study. He had received four intradermal injections

*We are indebted to Professor Felix Pinkus, Monroe, Michigan, for the preparation of the microphotographs.

of penicillin. Six days after the passive transfer test, he noticed severe itching at some test sites. At one of them an inflammatory wheal about 1 cm. in diameter with a flare one inch in diameter was present. Half

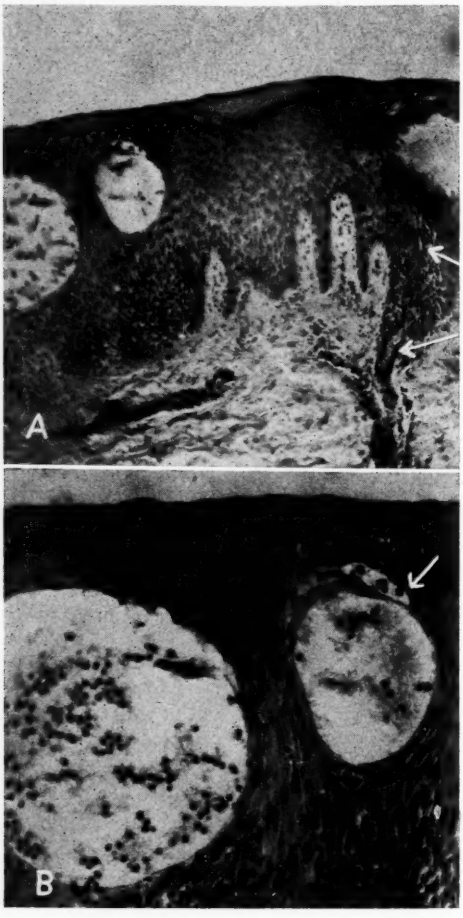

Fig. 4. (*A*) Vesicular "dysidrotic" dermatitis of finger following local application of penicillin. The vesicles apparently are located at the site of sweat gland ducts. One of these ducts leading down from the vesicle at the extreme right can be recognized in the papillary and subpapillary strata (see arrows). (*B*) There are flat shaped vesicular spaces above the middle vesicle possibly corresponding to the enlarged intra-epithelial part of a duct (see arrow). The connection of the large vesicle at the left side with the duct of a sweat gland was apparent from other sections.

an hour later a similar inflammatory, somewhat urticarial swelling with itching appeared at two more test sites, and several hours later the last test site showed a similar, though smaller, lesion. Twenty-four hours later

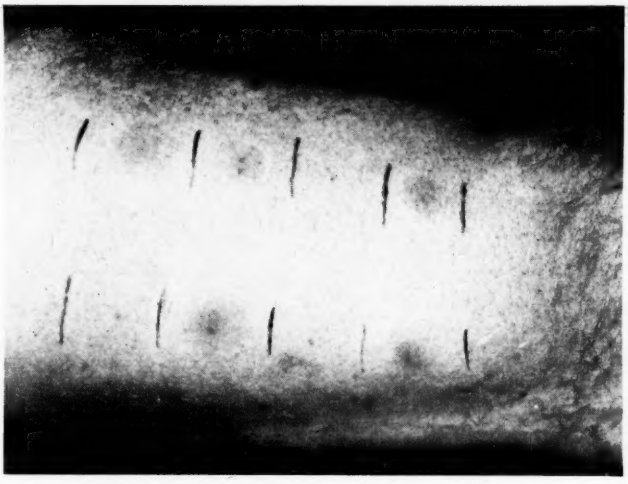

Fig. 5. Tuberculin-type reactions to various commercial penicillins in volunteer who had become sensitized following attempts at passive transfer. The sites where penicillin was combined with serum (see page 189) reacted earlier and more severely after twenty-four hours (upper row, sites 1 and 4, lower row, site 2 from the left). This picture was taken forty-eight hours after the test. At that time the differences had become less pronounced.

there was a definite reaction at all four sites which had received penicillin. Henceforth, all further injections of commercial penicillin (125 units to 500 units) produced tuberculin-type reactions (Fig. 5). They appeared within ten to eighteen hours and were accompanied by itching. These lesions began fading after forty-eight hours and turned into a superficial dermatitis which was present for two weeks.

Microscopic examination of such an experimental lesion twenty-four hours after the injection showed an acute localized inflammation of the corium corresponding to the tuberculin-type reaction:

"The epidermis is normal. At one spot in mid-corium there is a small hemorrhage and the whole surrounding area is diffusely infiltrated with grotesquely shaped nuclei, probably very actively motile leukocytes and possibly lymphoycytes. Other areas show narrow blood vessels which contain polymorphonuclear leukocytes and are surrounded by fairly heavy round-cell infiltration."

Another biopsy from a similar lesion was taken at a later stage, sixty hours after the injection. It presented the picture of a subacute, non-

specific inflammation of the corium (Fig. 6, *A*) plus an early "eczematous" reaction of the epidermis (Fig. 6, *B*):

"Most of the epidermis is normal, but there are some areas of spongiosis and a

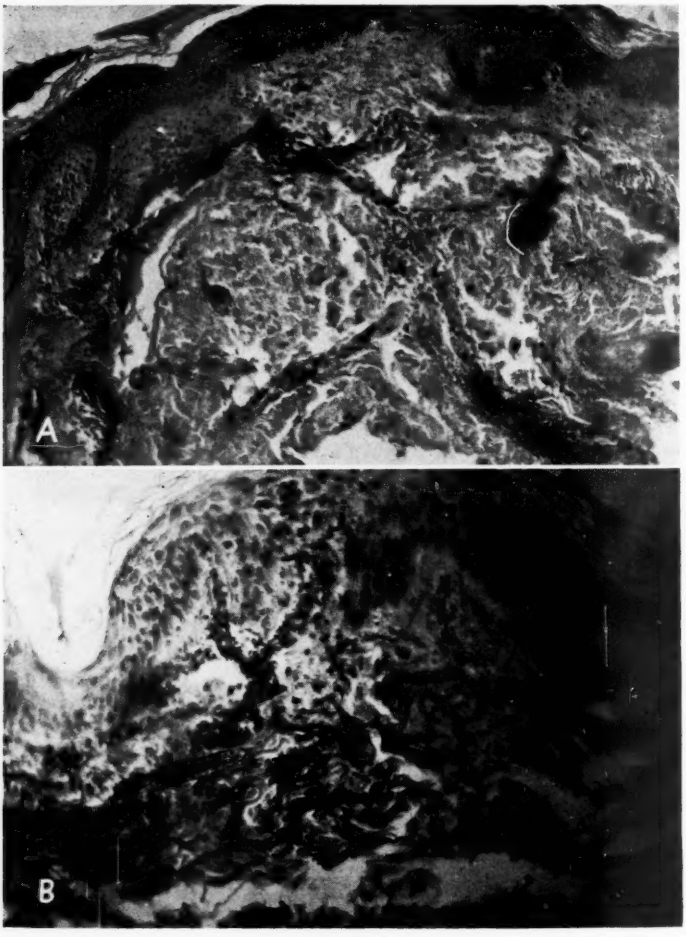

Fig. 6. (*A*) Tuberculin-type reaction from commercial penicillin in a volunteer. Biopsy taken after sixty hours. Non-specific inflammation of the corium. Most of the epidermis is intact. (*B*) Same lesion, different section. This picture shows one of the few areas with epidermal changes. Transmigration of leukocytes into the epidermis and "spongiosis" (at center and left side of the microphotograph).

few small vesicles. The horny layer is normal throughout. Practically all the blood vessels of the upper half of the corium are sheathed in rather heavy round-cell infiltrates. The vessels themselves are wide and filled with red cells. There is no unusual number of polymorphonuclear cells."

TABLE I. TUBERCULIN-TYPE SENSITIVITY VERSUS ECZEMATOUS CONTACT-TYPE SENSITIVITY

Type of reaction:	Tuberculin-type or Microbic-type reaction	Contact-type or "eczematous" reaction
Clinical lesion:	Papular lesion	"Eczematous" dermatitis
Pathologic characteristic:	Inflammatory	Inflammatory
Time of appearance of reaction:	"Delayed" (after 8 to 48 hours)	"Delayed" (after 8 to 48 hours)
Shock Organ:	Cutis	Epidermis
Antibodies:	Only fixed antibodies	Only fixed antibodies
Release of histamine or histamine-like substance:	Not demonstrated	Not demonstrated
Result of *in vitro* antigen-antibody reaction:	Damage to cells	Damage to cells
Relation of site of test to intensity of reaction:	Reaction stronger the closer to primary focus	Reaction stronger the closer to primary focus
Eosinophilia	O or +	O or +
Heredity	?	?

Intradermal tests with 250 to 1,000 units of crystalline sodium penicillin "G" did not produce any pathologic reactions. Unlike the original patient, this volunteer had not become sensitized to the crystalline penicillin, but to some impurity of the commercial products.

DISCUSSION AND COMMENTS

Immunologic Aspects of the Case—The case presented is interesting on account of the particular immunologic response of the skin. One might be inclined to classify our case as a contact dermatitis. Instances of local sensitivity of the skin from contact with penicillin have been reported previously, the first one by Pyle and Rattner.[2] These authors presented a true case of contact-type dermatitis. According to our present concepts, "contact-type" dermatitis is usually based on a delayed "eczematous" reaction of the epidermis, as evidenced by a positive eczematous reaction to a patch test. There can be no doubt that external contact was the cause of the dermatitis in our case. However, it is the type of reaction and the shock organ that determine "contact-type dermatitis," and not the avenue of the allergen. The latter may be brought in contact with the shock organ from without and within. Conversely, not all dermatitis that is brought about by external contact is immunologically "contact-type dermatitis." Our case seems based on the tuberculin-type of sensitivity and not the ordinary eczematous contact-type sensitivity. A comparison of tuberculin-type sensitivity and "eczematous" contact-type sensitivity is presented in Table I.

It becomes apparent from this table that tuberculin-type sensitivity and "eczematous" contact-type sensitivity share many characteristics. They

differ mainly in regard to the shock organ. Perhaps these two forms are identical in principle. In tuberculin-type sensitivity the shock organ is mainly the cutis; in eczematous contact-type sensitivity, chiefly the epidermis. That would account for their frequent association.† Still the difference of the shock organ constitutes reason enough for the distinction of the two types of sensitivity.

Tuberculin-type sensitivity to penicillin had been demonstrated previously by Rostenberg and Welch.[4,5] However, Rostenberg and Welch's patients did not suffer from a dermatitis. Our case represents an actual penicillin dermatitis based on tuberculin-type sensitivity. The patient responded with a papular cutaneous reaction to intradermal injections of penicillin. The existence of the tuberculin-type sensitivity was verified by the histologic study (Fig. 2). The negative patch tests with penicillin demonstrated the lack of general contact-type eczematous sensitization. The local application of penicillin to the previously diseased finger produced a vesicular "dysidrotic" dermatitis.

This is evidence of some localized epidermal sensitivity in addition to the underlying tuberculin-type cutaneous sensitivity. This observation seems to contradict the claim that the patient's dermatitis is based on tuberculin-type sensitivity. One might assume that this is an instance of true localized eczematous contact dermatitis, and the general tuberculin-type sensitivity may be just incidental. Such a conclusion is not warranted. Involvement of the epithelium does not necessarily make a dermatitis a "contact-type" dermatitis. I may recall that the superficial trichophytosis of the glabrous skin always produces epidermal changes in the form of spongiosis, frequently leading to intra-epithelial vesicles. Yet the generalized sensitivity in these cases usually is of the tuberculin type.

Our assumption that our case is based on tuberculin-type sensitivity rests also on the fact that the clinical picture corresponded perfectly to the vesicular dermatophytid of the hands which we see so often in patients with dermatophytosis of the feet. In both instances we find a grouped vesicular eruption, not a diffuse dermatitis. In both instances the lesions are located mostly around sweat ducts. In both instances there is a generalized tuberculin-type (dermal) hypersensitivity but no generalized epidermal sensitivity. In both instances there is a tendency to very localized epidermal sensitivity. In our patient, application of a penicillin solution produced an eruption only on previously affected fingers, and not on others. The tendency of some dermatophytids to recur regularly at the same sites is known.

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†Co-existing epidermal and non-atopic dermal sensitivity are encountered much more often than is generally recognized. It is not the purpose of this paper to go into general theoretical principles. However, their discussion is of great theoretical and practical importance in regard to certain forms of eczema, notably contact-type dermatitis and microbic (bacterial and fungous) eczemas. Studies on non-atopic dermal sensitivity, their implications and explanation, will be presented in forthcoming publications by one of us (S.E.): Studies in contact-type dermatitis.—I. Role of non-atopic dermal hypersensitivity in contact dermatitis.—II. "Dermitis": Dermatitis based on non-atopic dermal hypersensitivity.—III. Identity of dermal non-atopic sensitivity and tuberculin-type sensitivity. (To be submitted to the Journal of Investigative Dermatology).

These parallels justify the classification of our case as a dermatitis based on tuberculin-type sensitivity. It seems probable that some of the vesicular id-like eruption encountered not infrequently in sensitivity to parenteral penicillin[1] can be explained on the same basis. There exists also a practical angle. Our case demonstrates that one may deal with a dermatitis by local contact where patch tests may be negative on normal skin. The generalized tuberculin-type sensitization demonstrates that this was not just a matter of local sensitivity. Such an occurrence apparently is not unique. Similar observations have been made with other "contact" allergens, notably drugs.‡

REMARKS ON EXPERIMENTAL SENSITIZATION TO PENICILLIN

The accidental experimental sensitization to penicillin observed in the volunteers who submitted to the passive transfer test confirmed largely the experiences of Rostenberg and Welch[5], although their cases became sensitized to crystalline penicillin, whereas our volunteer apparently became sensitive to some impurity of the commercial penicillin. Our experiments also indicated that the preceding injection of blood serum enhanced both the chance of sensitization and the degree of reaction, as had been noted by Rostenberg and Welch.[5] Out of the four volunteers for the passive transfer, two became sensitized. Furthermore, in the sensitized person injections of serum and penicillin led to an earlier appearance and a more intensive reaction than injection of penicillin alone. Whether serum and penicillin were injected simultaneously or whether the penicillin test followed the serum injection by twenty-four hours made no difference. The stimulating effect of homologous serum on sensitization to drugs is known from previous experiments of Frei and Landsteiner, who demonstrated that guinea pigs could be sensitized much more easily to neoarsphenamine when the drug was mixed with guinea pig serum. The relative ease of sensitization to penicillin by intradermal injections, especially in conjunction with serum injections, should caution against indiscriminate skin testing with this drug. When passive transfer is attempted, the recipients should be warned about the danger of sensitization because sensitization to penicillin may be a great handicap to the sensitized person.

SUMMARY

A case of a vesicular dermatitis of the hands due to external contact with penicillin is presented. The patient was generally sensitized to penicillin, both commercial brands and crystalline penicillin "G". Only intradermal

(Continued on Page 220)

‡In these instances also patch tests were negative, but severe tuberculin-type cutaneous reactions to the same allergens could be demonstrated. These observations will be reported elsewhere (see footnote†, page 194). They should teach us that a negative patch test to a substance cannot be trusted when the clinical picture or course suggests hypersensitivity to the same agent. As a word of warning, I may add that if intradermal tests with contact allergens are performed, much weaker concentrations must be used than for patch testing. For instance, for nickel sulfate a 5 to 10 per cent aqueous solution is recommended for patch testing (3); for intradermal tests 0.02 c.c. of a 1:40,000 dilution in normal saline appears the proper dose.

REACTIONS TO PENICILLIN

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As has been so well stated by Brown[3] recently, the reactions to penicillin now are beginning to pour in with its more widespread use. He quotes Pyle and Rattner[9] as describing a contact dermatitis occurring in a medical officer who prepared and administered penicillin solution. There was marginal conjunctivitis spreading to the bridge of the nose and forehead and the central portions of the face with eczematous lesions on the hands and penis. All eruptions disappeared on cessation of contact and reappeared as soon as re-exposure occurred. Patch tests were strongly positive.

Brown[3] also reviews the following cases: One, a chemist described by Silvers[11] was engaged in research. An itchy rash appeared on the eyelids and penis after one year's exposure with complete disappearance as soon as direct contact with penicillin ceased. Brinkley and Brockmole's[2] patients were both physicians handling penicillin. In one, the eruption appeared on the forehead and forearms with a positive patch test. In the second the rash was thought to be a seborrhoeic dermatitis. Patch test here was negative but eruptions of hands and feet occurred following an injection of 60,000 units. In both cases eruption disappeared on avoidance of contact with the drug. Barker[1] describes a medical officer dispensing penicillin solution. The lesion was an acute dermatitis of the face and neck. His second case responded to penicillin injections with dermatographia plus large confluent wheals on trunk and extremities. In both cases patch tests reproduced the original lesions. Freyhan's[5] patient developed a severe generalized pruritus for five days after 100,000 units of penicillin over a period of ten days. Criep's[4] case developed a generalized urticaria after 200,000 units over fourteen days. On this patient direct intradermal skin tests, passive transfer and precipitin tests were positive with penicillin solution.

Keefer[7], writing in 1943, remarks: "One of the remarkable features of penicillin is its low toxicity and the extremely low incidence of a systemic nature." In 500 cases, urticaria was reported in only fourteen cases with thrombophlebitis (at the site of injection) and occasionally chills and fever. Writing again on this subject in 1945, Keefer[6] mentions urticaria in 2 to 5 per cent and occasionally attacks of vesicular eruptions. He states: "At present we have seen one severe rash of this type. There are no known contra-indications to the administration of penicillin." Lyons[8] found three types of complication to penicillin therapy. First, urticaria in 5.7 per cent of 209 cases. This usually occurred during the course but could come on as late as nine days after treatment. He found that subsequent courses of treatment with penicillin in these patients

who developed urticaria were uneventful and not associated with a recurrence of the skin lesion. With the urticaria may appear abdominal cramps and fever. Secondly, transient azotemia and thirdly, thrombophlebitis was frequent at the site of I.V. injection.

Rotenberg and Welch[10] found that 5.5 per cent of 144 individuals who had no previous contact with penicillin reacted with a tuberculin type of lesion when given 1/10 c.c. containing 1,000 units of penicillin intradermally.

They then injected intradermally nine patients with 10,000 units of penicillin, 1,000 units in 0.05 c.c. of saline in ten different sites. These injections were repeated in approximately the same areas five days and ten days later, a total of thirty injections. One of these patients developed urticaria, dermatographia, lacrimation and conjunctival injection. In this case, as in all those in which the hypersensitive state had been induced by intradermal injection, the passive transfer test was negative.

Case 1.—Corporal C. P. H., twenty-nine years old, had been handling penicillin in the V.D. Clinic for six to eight months. Family and personal histories were negative for allergy. He first developed a scaling lesion on the left hand in July, 1944. This had cleared up entirely upon his return from a fourteen-day furlough. It again appeared on the left hand on resumption of penicillin handling and continued thus until December, 1944.

On December 15, 1944, intradermal skin test (100 units) and patch test were markedly positive. After this he continued working in the clinic but used a rubber glove on his left hand. On December 22, he developed generalized severe urticaria of arms, thighs and buttocks with angioneurotic edema of entire face (especially the eyes). This reaction continued for about seven days and did not clear entirely until January 3, 1945, thirteen days after the onset. The left hand still had a little scaling dermatitis. Routine intradermal tests in the allergy clinic were all negative.

Although he was taken off the job of handling penicillin, the left hand again developed a moderately severe dermatitis three days later, and this time he was hospitalized for twenty days. During this stay in the hospital a passive transfer was markedly positive. Nine months later the passive transfer test was negative but the intradermal skin test with 100 Oxford units of penicillin gave a tuberculin type of reaction two days after injection, similar to that described by Rotenberg and Welch.[11] Also the patch test showed a definite scaling five days after application of the patch.

Case 2.—Lt. J. H. M. gave a history of occasional mild bouts of hives in civilian life. He had a localized skin rash on both hands in 1943 while taking a sulfonamide for a draining left ear. The latter had been draining for several years off and on. From July 7, 1945, to July 22, 1945, he was given daily local applications of penicillin to this left ear canal. On August 6, penicillin intramuscularly (20,000 units every four hours) was started and continued until he had a total of 520,000 units. On August 7, 1945, sulfadiazine (Gm. 1.5 every four hours) was started but on the following day this was discontinued due to the appearance on the hands of a nodular itching eruption resembling the lesions that were present in 1943 on taking a sulfonamide. This present rash disappeared twenty-four hours after discontinuing the sulfadiazine. The penicillin was discontinued on August 11 with improvement noted in regards to ear drainage. Nine days after

this drug was stopped the patient developed a severe and painful swelling of his knee, foot, ankle, and wrist joints with angioneurotic edema of face and eyes and generalized severe urticaria, the latter often iris-like in character. All of these lesions remained severe for approximately six days in spite of therapy and then subsided rather abruptly followed by exfoliation of both hands. He was then tested intradermally with 400 units penicillin with moderately positive results. The patch test was fleetingly positive (the hive lasting only twenty to thirty minutes). A passive transfer test was markedly positive. Eleven weeks later the intradermal and passive transfer tests were negative but the patch test was still positive, giving now a vesicular and later scaling lesion under the patch. The left ear was still draining slightly.

DISCUSSION

While many writers on the use of penicillin (and certainly the literature put out by the manufacturers) skim lightly over the reactions to this drug, it can be seen from some reports, including the two cases cited in this paper, that these reactions can be quite severe. In the first place, in both of the cases it will be noted that previous contact (in Case 1 of long duration) was of definite importance as a sensitizing mechanism. It makes one wonder about the wisdom of the increasing widespread use of this valuable therapeutic agent in minor ailments for, if sensitization occurs, we may be denying its use to the patient in instances where it is specific and life saving. Secondly, the passive transfer and patch tests seem to be of value in proving the etiological factor where penicillin is concerned. This is in contrast to Rotenberg and Welch's findings where the passive transfer test was consistently negative. Thirdly, it will be noted that in Case 2 there was a gap of fourteen days between the first and second administrations of the penicillin. This brings to mind the danger of reaction incurred in the use of sulfonamides where a gap of over seven days is allowed to elapse between close courses of therapy. Lastly, after nine and approximately four months respectively, in the cases cited, patch and intradermal tests were still positive although the passive transfer had become negative.

SUMMARY

Two cases of severe reaction to penicillin are added to the mounting series of untoward effects from this drug. Passive transfer, patch and intradermal skin tests seem to be of value in determining the etiology. Sensitivity can apparently remain, as determined by these tests for months after the reaction, indicating that caution should be taken if they are to be used again following a severe reaction.

REFERENCES

1. Barker, A. N.: Allergic reactions to penicillin. Lancet, 248:177-178, (Feb. 10) 1945.
2. Binkley, G. W., and Brockmole, A.: Dermatitis from penicillin. Report of

(Continued on Page 225)

COMBINED PENICILLIN AND HYDROGEN PEROXIDE AEROSOL THERAPY IN LUNG INFECTIONS

Preliminary Report

By HAROLD A. ABRAMSON, M.D., F.A.C.A.
New York City

IT was previously shown by the writer[2] that by means of a simple commercial nebulizer (De Vilbiss No. 40), hydrogen peroxide solutions up to approximately 4 per cent (12 per cent urea peroxide in a 50 per cent glycerol solution) could be readily nebulized and remain fairly stable in the air of a small closed room. These hydrogen peroxide aerosols could be breathed in concentrations up to 3 per cent for short periods without much irritation. Both normal and allergic subjects could remain in a room filled with an atmosphere of these peroxide aerosols without discomfort. It was revealed that there were two important ways of using these aerosols in medicine:

1. As a germicidal aerosol similar to those studied by Twort and his group.[14]

2. Directly as an aerosol for local therapy in the lungs, similar to the use of epinephrine salt solution aerosol for the relief of bronchial obstruction and more analogous to the recent application of penicillin aerosol first published by Bryson, Sansome and Laskin.[5]

War activities of the writer prevented further exploration of the properties of these hydrogen peroxide aerosols until recently. It seems appropriate now to publish a preliminary report on progress made along the lines of therapeutic application. Bryson and Reese, under contract with the Technical Division, Chemical Warfare Service, at the Cold Spring Harbor Laboratory, will shortly publish data on the properties of germicidal hydrogen peroxide aerosols.[4]

THERAPEUTIC AEROSOLS

Hydrogen peroxide, as a drug and antibiotic in aerosol therapy of the lungs and bronchi, might have therapeutic possibilities not possessed by penicillin which affects mainly Gram-positive organisms. Since streptomycin is not available[6] in large quantities, the exploration of the use of hydrogen peroxide as a general antibiotic agent for topical treatment of the lungs seemed desirable.

Animal Experimentation.—Mice were exposed to aerosols (particle radii: $<2\mu$ containing 3 per cent hydrogen peroxide nebulized from a solution of 9 per cent urea peroxide) for two hours a day for seven days

From the Biological Laboratory, Cold Spring Harbor, Long Island, New York
This investigation was aided in part by a grant from the Josiah Macy, Jr., Foundation, New York, and the Asthma Research Foundation, Boston.
The author is indebted to Dr. Vernon Bryson for his aid in the course of this study.

by means of De Vilbiss or Vaponephrin nebulizers operating between four and eight liters per minute. Except for minor irritation, twitching of the nose and huddling, there were no signs of the animal's being exposed to any unusual injury. As a matter of fact, an isotonic saline aerosol may produce the same symptoms. At the end of seven days, certain of the mice were sacrificed and compared with controls. There were no gross abnormalities in the lungs or in any of the other organs. The tissue sections have not as yet been studied.

Human Tests (Normal Respiratory Tract).—Before using peroxide aerosols on patients, volunteers breathed increasing quantities of urea peroxide aerosol. Both the De Vilbiss No. 40 and the Vaponephrin nebulizers were employed. The mist was delivered only during inspiration. No significant difference between the effects of the nebulizers was observed, as far as irritation of the upper respiratory tract was concerned. Following is an example of the type of experiment performed:

Subject H.A.A.—Nine per cent urea peroxide solution, plus 10 per cent glycerol dissolved in physiologic saline, was nebulized seventeen and a half minutes during the inspiration phase only. The De Vilbiss No. 40 was employed without rebreathing. The volume velocity of the compressed air used to generate the aerosol was approximately six liters per minute. The total peroxide solution nebulized was 2.1 c.c. Although this solution contained 3 per cent hydrogen peroxide, there was no irritation of the upper or lower respiratory tracts, nor did any symptoms occur twenty-four hours later.

Other similar experiments indicated that with certain precautions hydrogen peroxide aerosols could safely be used in man.

Administration of Hydrogen Peroxide Aerosol in Clinical Conditions Technique.—Either compressed air from a tank or from a compressor may be used. Oxygen in large tanks is convenient and in some ways preferable. The tanks should be equipped with a volume velocity gauge. The air flow should be regulated to the output desired and for the type of nebulizer employed. In general, between 4 and 8 liters per minute with the De Vilbiss No. 40 or the Vaponephrin nebulizer has been found suitable. The small stopper should be left in the vent opening. The reader is cautioned against directing the blast from the tip of the Vaponephrin nebulizer directly against the soft palate. The patient should be warned against placing the long tip of the Vaponephrin nebulizer all the way back in the mouth because the back of the throat or the soft palate acts as a baffle. This difficulty is not encountered in the use of the De Vilbiss No. 40 nebulizer which has a short tip.

The writer knows of no published scientific evidence which supports the point of view that rebreathing is essential. Indeed, since in rebreathing the patient breathes the directly nebulized mist only once every other

breath, the method of treatment becomes unduly prolonged. Olsen, who has published an extensive series of cases with excellent therapeutic results, applied the nebulizer directly to the mouth without other equipment, as advocated by Bryson and his co-workers.

A very simple cut-off can be obtained by merely boring or cutting a small hole about 5 millimeters in diameter in the tubing which connects the nebulizer to the oxygen tank. By this technique the usual glass Y tube is eliminated and the patient merely places his finger over the hole in the tube near the nebulizer (2 inches) at the beginning of each inspiration. It is important to stress to the patient that the early part of inspiration is most important for it is this phase which brings the air to the deep recesses of the lungs. In practice, the patient is coached with the word "in," indicating that the patient should breathe in, and "out," with the instructor making certain that the finger is placed on the cut-off just before the word "in" is used.

There is, of course, no reason, except economy, why a continuous generation of aerosol should not be employed. Although a continuous generation is wasteful of antibiotic material, it is insurance against faulty technique on the part of the patient. Masks also may be used to connect the patient directly with the nebulizer. Whether or not masks are desirable routinely must be determined by future quantitative experimental work. A careful study is that of Mutch and his co-workers. Their work will be reviewed elsewhere.

To summarize, then, all that is needed for penicillin aerosol therapy of the average ambulatory or hospitalized patient (or combined penicillin and hydrogen peroxide aerosol therapy of the lungs) is a source of compressed air or oxygen, a piece of rubber tubing and a suitable nebulizer. Rebreathing equipment is not required. Indeed, it is undesirable because of the prolonged therapy usually desired. The use of nasal tips for aerosol therapy of the lungs, plus rebreathing bag, is still open to question. How much penicillin is absorbed by the nasal mucosa and pharynx and how much is applied to those parts of the lungs where topical therapy is desired has not yet been published for equipment of this type. On the basis of the simplest type of aerodynamic reasoning, the less equipment between the nebulizer and the patient, the less turbulence will occur and the greater is the probability of the nebulized material being carried by convection into the lungs. It is this principle of *direct application of the aerosol to the rush of inspiratory air which is basic in aerosol therapy of the lungs.* It is this method which is recommended by the writer until suitable evidence to the contrary is provided by those advocating otherwise.

ILLUSTRATIVE CASE REPORTS

Asthma: Allergic in Origin.—A woman, aged fifty-four, who had asthma for twenty years and had periodic attacks of asthma complicated by very mild myocardial insufficiency was given hydrogen peroxide aerosol for ten minutes as

9 per cent urea peroxide plus 10 per cent glycerol in physiological saline. The patient complained of very slight irritation, but in spite of the fact that 3 per cent hydrogen peroxide was administered, there was no cough, no irritation of the throat and no induction of an asthmatic attack.

Asthma Complicated by Infectious Bronchitis.—This patient, a woman, aged forty, was admitted two weeks before the initiation of hydrogen peroxide aerosol therapy to the hospital with respiration of 60 per minute, a temperature of 101 and a pulse of 120. X-ray study of the chest was essentially negative. During the following two weeks her asthma decreased considerably except for a sudden rise in temperature to 104 degrees which persisted only one day and disappeared after coughing up considerable mucus. The patient's general health and pulmonary condition improved. However, a persistent low-grade temperature, reaching 100.5, remained.

At this time the patient was given 1.3 per cent hydrogen peroxide as an aerosol plus 10 per cent glycerol solution in isotonic saline. This was administered for six hours per day for three days, ten minutes every hour. The total time that the patient received hydrogen peroxide aerosol was sixty minutes per day. A De Vilbiss No. 40 nebulizer was used. At the end of three days there was a slight irritation in the throat which, however, was relieved by washing the mouth and throat with physiological saline. The therapy was continued for four days. During this time the temperature gradually returned to normal. However, when peroxide was withdrawn, the low-grade temperature recurred. Immunological tests for brucellosis, typhoid, paratyphoid and infectious mononucleosis were negative. It is impossible to state whether the peroxide was responsible for the reduction in the patient's temperature. After thirty-one days of hospitalization, the patient returned home. Three weeks after reaching home her low-grade fever occasionally recurred and there was some exudative bronchitis. This patient was subsequently treated with combined therapy of penicillin aerosol alternately with urea hydrogen peroxide aerosol, shifting the antibiotics every two days. The routine advocated by Olsen[11] was employed for penicillin. The patient received 5000 units of penicillin as an aerosol every ten minutes for ten hours a day so that the lungs were exposed to five hours of penicillin aerosol per day. Penicillin was administered for two days, then withdrawn, and hydrogen peroxide aerosol, as 3 per cent urea peroxide plus 10 per cent glycerol dissolved in physiological saline, followed ten minutes every hour for seven hours per day. After two weeks of therapy, there was a marked decrease in bronchial exudate. The asthma persisted but was decreased in severity.

Bronchiectasis (Suppurative).—Combined therapy of penicillin and hydrogen peroxide aerosols, as indicated in the foregoing, with some modification is being employed by the writer in suppurative bronchiectasis. In the cases studied thus far, because of the dominance of Gram-positive organisms, the penicillin aerosol is continued three to seven days with hydrogen peroxide aerosol (urea peroxide 3 per cent plus 10 per cent glycerol in physiological saline) subsequently administered for two to three days. It may be recalled that the presence of glycerol diminishes the throat irritation, makes the peroxide aerosol more palatable and stabilizes the mist. I am indebted to Drs. George Baehr and Arthur S. Touroff for the courtesy of treating the following case which has come to operation:

This was the case of an obese woman, aged thirty-nine, with a fourteen-year history of intercurrent suppurative pulmonary disease. Physical examination, as well

as x-ray report and laboratory data, revealed suppurative bronchiectasis with cavitation of the right middle lobe. About 50 c.c. per day of odoriferous purulent material were expectorated. Penicillin aerosol was begun on March 2, 1946. Penicillin was then discontinued on March 6 and urea peroxide aerosol was administered for two days. On March 8, penicillin aerosol was resumed. On March 14, pus was still present on bronchoscopy. On March 18, penicillin aerosol was applied until March 21 when penicillin was instilled directly into the cavity of the right middle lobe by Dr. Bender, as advocated by Siltzbach.[13] Similar instillations were made daily through the bronchoscope up to March 26. Approximately 100,000 units per day in 4 c.c. of saline were administered. On March 30, because of the rapid improvement of the patient since the beginning of combined penicillin aerosol, hydrogen peroxide aerosol and direct installation therapy, the patient was deemed ready for operation, and right middle lobe lobectomy was performed by Dr. Touroff.

Following are the findings and procedure of Dr. Touroff:

A right-sided submammary incision was made and the 4th rib exposed from the region of the sternum well into the axilla. The costal cartilage was divided close to the sternum and the thorax entered through the 4th intercostal space. Extensive adhesions were found between the involved middle lobe and the adjacent upper and lower lobes and between the lobe and the chest wall. After dividing numerous broad adhesions, the middle lobe was exposed. It was completely airless and was markedly shrunken in size. It was bluish red in color and quite indurated. It measured roughly 3 x 3 x 4. By blunt dissection, the middle lobe was separated from the adjacent lower lobe and the pericardium. Numerous vascularized adhesions were divided and the bleeding points ligated. The fissure between the upper and middle lobes was incomplete, so that in order to free the middle lobe, it was necessary to divide the pulmonary tissue of the adjacent portion of the upper lobe. After the latter had been accomplished, the defect in the upper lobe was closed with a series of mattress sutures of catgut. A typical dissection lobectomy of the middle lobe was performed. The hilar structures were closed with fine mattress sutures of chromic catgut and the stump was buried by uniting the remaining small amount of pulmonary tissue at the hilus over it with interrupted mattress sutures. On inflating the lung with positive pressure the upper and lower lobes almost completely filled the dead space which was left by removal of the middle lobe. 200,000 units of penicillin were instilled in the fifth intercostal space anteriorly. At the conclusion of operation patient was bronchoscoped on the operating table and only a small amount of dried blood was noted in the lower branches of the bronchial tree, on both sides. Patient left the operating room in good condition.

It should be noted that according to Dr. Touroff, the lung was "dry" on operation. A similar opinion was expressed by the pathologist who reported "chronic pneumonitis and bronchiectasis."

Tuberculosis.—Combined penicillin and hydrogen peroxide aerosol therapy is being used to study the effect on both the primary and the secondary infection in pulmonary tuberculosis. These clinical trials, together with animal experimentation, will be reported in detail in future communications.

DISCUSSION

The case histories described in the foregoing are merely representative of the type of therapy now being investigated by the writer. No conclusions can be drawn as yet as to the efficacy of combined penicillin and hydrogen peroxide aerosol therapy as described in the foregoing. It is un-

fortunate that penicillin is destroyed by many oxidizing agents because, if this were not so, both penicillin and hydrogen peroxide could be nebulized simultaneously and both antibiotics applied topically to the lungs at the same time. In this way, the synergistic action of each on the other might have provided markedly enhanced germicidal activities.

Since it appears that penicillin remains in the lung tissues for some time, the possibility of synergism is not ruled out by our method of therapy. It is quite possible that exceedingly small amounts of penicillin retained by organisms might render them more susceptible to the action of peroxide. And, vice versa, organisms exposed to small amounts of peroxide might be rendered more susceptible to penicillin. Indeed, the interplay of germicidal activity of antibiotics of this type furnishes a complicated but hopeful approach to the therapy of bacterial and virus infections of the lung.

That the use of peroxides may be of greater importance in the therapy of infections other than hitherto believed has been recently emphasized by the paper of Keilin and Hartree.[9]

Keilin and Hartree point out that the function of catalase within the cell may not merely be protective. Their idea is supported by the fact that (a) H_2O_2, formed in a primary oxidation reaction, may oxidize hemoglobin within mammalian red blood cells, even though excess catalase is present; (b) a very small concentration of H_2O_2 (one in four million) is toxic to various micro-organisms, even though catalase is present within the cells.

The presence of catalase within cells, therefore, does not constitute a definitive block to the antibiotic activity of H_2O_2. The possibility exists, however, that anticatalase may accelerate the reaction velocity in which H_2O_2 acts as an antiseptic. The search for anticatalase will be part of our aerosol therapy program.

Another interesting aspect of the potential application of H_2O_2 aerosol is that H_2O_2 at body temperature has a significant vapor pressure. In other words, when an H_2O_2 aerosol is inspired, H_2O_2 gas exists within the lungs and it should diffuse very rapidly, indeed, to points inaccessible to larger liquid masses. It is conceivable that H_2O_2 gas itself may be used for the therapy of lung infections.

The argument has frequently been raised to the writer that it did not seem likely that aerosol droplets could get to the interior of most pathological lesions in the lung. It is certainly true that when a mechanical block exists ordinary particles cannot get past a block. However, topical therapy of the lung is designed for several purposes: (a) protecting normal lung tissue from spread of infection, (b) walling off the infected areas already existing and, finally, if possible, (c) bringing the germicidal aerosol or gas directly to the site of the bacterium or virus producing the disease to destroy primary and secondary invaders of the living tissues. That this concept has been justified is well brought out by the successful results achieved in aerosol therapy of the lungs and bronchi.

SUMMARY

1. Hydrogen peroxide solution, plus 10 per cent glycerol in physiological saline, may be readily nebulized without loss of stability, whether used as hydrogen peroxide directly or as urea peroxide.

2. These solutions may be administered to both animals and man in germicidal concentrations without appreciable irritation.

3. Preliminary data on animals indicate that even when hydrogen peroxide aerosols of the type described are administered over prolonged periods, neither the lungs nor the eyes are damaged.

4. A brief report is made on the effect of administering hydrogen peroxide (urea peroxide) aerosols in cases of asthma, asthma complicated by infectious bronchitis and bronchiectasis with lung abscess. In these cases, not only was hydrogen peroxide (urea peroxide) aerosol used alone, but it was also combined alternatingly with penicillin aerosol. The use of combined penicillin and hydrogen peroxide aerosols provides a method of approach to the destruction of both Gram-positive and Gram-negative organisms with readily available antibiotic material.

5. A program is outlined in which combined penicillin and urea peroxide aerosol therapy, as described in the foregoing, is being applied to retard primary and secondary infections in pulmonary tuberculosis.

ADDENDUM

Since the preceding paper was submitted for publication, the undersigned would like to report on progress made in the effect found on both primary and secondary infections in pulmonary tuberculosis during the past month by the use of penicillin and hydrogen peroxide aerosol therapy, applied as described in the preceding paper.

Two typical chronic advanced cases whose pulmonary lesions had remained stationary for months without material clinical symptoms, except irritating paroxysmal cough and positive sputum, have been treated for one month.

Case 1, with laryngeal involvement:

(a) The laryngeal pain was relieved by penicillin aerosol almost immediately.

(b) The cough has improved, being less forceful and not distressing to the patient.

(c) The purulent character of the sputum has decreased, with a decrease in viscous quality.

(d) Gram-positive organisms have disappeared from the sputum on culture. A Gram-negative bacillus remains on culture.

(e) The hydrogen peroxide aerosol does not increase the cough even though slight irritation of the back of the throat may occur after two days' use.

(f) Penicillin controls the usual cough although it is not certain whether this is due to the penicillin or the liquid contained in the aerosol.

(g) X-rays of the chest disclose no material difference.

(h) Sedimentation time essentially unchanged.

(i) Penicillin excretion—On the basis of occasional assays obtained thus far, at least 3,000 units of penicillin have been excreted per day. Levels up to 1.2 units of penicillin per c.c. of a twenty-four hour urine specimen have been found. This would make the twenty-four hour excretion over 3,000 units.

(j) Tubercle bacilli are still present in the sputum on smear and culture.
(k) There has been a material improvement in the previously severe cough.

Case 2:

(a) The cough has improved as in Case 1.
(b) The purulent character of the sputum has decreased as in Case 1.
(c) Gram-positive organisms have disappeared from the sputum on culture smears of the sputum. A Gram-negative bacillus remains on culture.
(d) The hydrogen peroxide aerosol does not cause irritation by increase of cough.
(e) X-rays of the chest are essentially unchanged.
(f) Sedimentation time essentially unchanged.
(g) Tubercle bacilli are present in the sputum on smear and culture.

To summarize, two typical chronic advanced adult cases of tuberculosis have been treated for one month by alternating penicillin and hydrogen peroxide aerosol therapy of the lungs. Although the sputum of both has remained positive for tubercle bacilli, most of the other organisms have disappeared on culture and there has been a material decrease in the severity of the cough.

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BIBLIOGRAPHY

1. Abramson, H. A.: Improved inhalation therapy of asthma. Arch. Phys. Therap., 21:612, 1940.
2. Abramson, H. A.: A stable hydrogen peroxide aerosol. Science, 96:238, 1942.
3. Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T., and Soroka, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectases and lung abscess: Preliminary report. Ann. Int. Med., 22:482, 1945.
4. Bryson and Reese: Unpublished data.
5. Bryson, V., Sansome, E., and Laskin, S.: Aerosolization of penicillin solution. Science, 100:33, 1944.
6. Editorial: J.A.M.A., 130:939, 1946.
7. Hagens, E. W., Karp, M., and Farmer, C. J.: Inhalation method for penicillin therapy: Preliminary report. Arch. Otolaryng., 41:333, 1945.
8. Hanks, R. J.: Nebulized penicillin in treatment of respiratory infections. Texas State J. Med., 41:253, 1945.
9. Keilin, D., and Hartree, E. F.: Bioch. J., 39:293, 1945.
10. Mutch, N., and Rewell, R. E.: Penicillin by inhalation. Lancet, 1:650, 1945.
11. Olsen, A. M.: Nebulized penicillin: Preliminary report of its role in the management of surgical bronchiectases. Proc. Staff Meet., Mayo Clin., 20:184, 1945.
12. Segal, M. S., and Ryder, C.: Penicillin aerosolization in the treatment of serious respiratory infections. Preliminary report. New England J. Med., 233:747, 1945.
13. Siltzbach, L. E.: Penicillin therapy in a case of chronic suppurative bronchiectasis. J. Mount Sinai Hosp., 12:825, 1945.
14. Twort, C. C., Baker, A. H., Finn, S. R., and Powell, E. O.: The disinfection of closed atmospheres with germicidal aerosols. J. Hyg., 40:17, 1940.
15. Vermilye, H. N.: Aerosol penicillin in general practice. J.A.M.A., 129:250, 1945.
16. Wilson, C. E., Hammond, C. W., Byrne, A. F., and Bliss, E. A.: The control of experimental pneumonia with penicillin. 1. Comparison of inhalation and injection therapy. Bull. Johns Hopkins Hosp., 77:411, 1945.

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HYDATID ALLERGY

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MOST patients with an Echinococcus granulosus cyst (hydatid cyst) give a positive allergic reaction when injected intracutaneously with the fluid of cysts. This reaction was described and used as a diagnostic method by Casoni[6], who injected 0.50 ml. of hydatid fluid intracutaneously in the forearm and observed the reaction produced twelve to twenty-four hours later. At the present time, only 0.10 ml. of hydatid fluid is injected in the skin.

Casoni's reaction is characterized by an erythema and swelling due to edema and to infiltration of the skin with eosinophiles.

Aside from the Casoni or delayed reaction, the injection of hydatid fluid can produce an early histamine-like reaction in patients with hydatid cyst, which was described by Pontano.[48] This early reaction generally appears from five to fifteen minutes after the intradermal injection of 0.10 ml. of fluid and is found positive in 90 per cent of patients with hydatid disease.[14,33,34,35,37] The Casoni or delayed test is found positive in a smaller percentage of cases. When a rupture of the cyst occurs or a suppurative process develops in the cyst in general, a positive delayed reaction is not found, but there is an early skin reaction, and a very definite positive fixation of complement occurs in the serum.[16,37]

Early positive reactions to hydatid fluid may be present in patients without hydatid cysts, but who have asthma, icterus, urticaria, dermographism[15,37], and liver carcinoma[39], and in patients with other parasitic diseases, especially *Taenia saginata* and *Taenia solium*.[8,41] In accord with my experience, a delayed positive reaction is present only in patients with hydatid cysts.[25]

Generally a positive skin reaction to hydatid fluid becomes negative two months after the extirpation of the cyst, but in some cases, a positive reaction may persist for several years after its removal.[45,57] The greatest percentage of positive skin reactions is found when the hydatid cyst is located in the liver or in the lung; negative reactions are very often found when the cyst is located in the brain or in the bones.

The skin reaction in hydatid disease is due to a reaction between the antigenic substances present in hydatid fluid and the reagins fixed in the skin cells. The serum of some patients with hydatid disease is found able to transfer the hydatid sensitiveness to normal individuals.[49] In accord with my investigations, while hydatid fluid can produce positive skin reactions in many patients, these reactions are not often transferable by the Prausnitz-Küstner technique.[25]

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THE ANTIGENIC SUBSTANCES OF HYDATID FLUID

In the investigation of skin tests, the fluid of cysts of *Echinococcus granulosus* from four sources may be used: sheep, calf, pig and human being. After sterilization by Seitz filtration, phenol or merthiolate is added to the fluid as a preservative. It is recommended pooled samples from several sources be used and a clinical control be run in order to be sure of the antigenic power of the liquid.[17] Two antigenic substances have been obtained from the hydatid fluid: a protein by adding 5 per cent trichloroacetic acid[11] and a polysaccharide by adding alcohol to a 50 per cent concentration final to the deproteinized fluid.[47,54] These two antigenic substances can be obtained also from the membrane of the cysts.[46] The protein is the best antigenic substance in the ability to produce skin reactions, while the polysaccharide is a poor antigen.[46] The ability of hydatid fluid to produce skin reactions is not altered by heating to 95° C.[36]

EOSINOPHILES IN THE BLOOD

In this parasitic disease an increase of the blood eosinophiles is often found. This increase may be as high as 25 per cent, and the eosinophiles return to the normal amount after the extirpation of the cyst.[52] When patients with hydatid cysts are injected intradermally with hydatid fluid, a great increase of eosinophiles in the blood is observed twenty-four to forty-eight hours later, which is of diagnostic significance because it is not produced in persons without hydatid cysts.[1,3,4,5] This particular reaction also can be observed in patients after the extirpation of the hydatid cyst.[1] An infiltration of eosinophiles is produced at the point of a positive skin reaction.[3,56]

I have confirmed all these observations[22,23], and I have given particular diagnostic significance to the increase of eosinophiles, because no increase is produced in patients without hydatid cysts, in spite of injections of very large amounts of hydatid fluid. Unfortunately, in many patients with hydatid disease this eosinophilic reaction is not produced after the injection of hydatid fluid.

REACTION OF GHEDINI-WEINBERG

Ghedini[18] and later others[32,58,59,60] showed that the serum of patients with hydatid cysts gives a positive reaction of fixation of complement using hydatid fluid as the antigen.

When a rupture of the cyst or a suppurative process is developed inside of the cyst, the reaction of Ghedini-Weinberg becomes intensely positive.[16] In some patients with a negative complement fixation and a positive intradermal reaction, the first reaction becomes positive twenty-four hours after the intradermal[39] or subcutaneous[1] injection of small amounts of hydatid fluid. This particular anamnestic reaction has been found by me in three of six cases[22,23] studied in these conditions.

HETEROPHILE ANTIBODIES IN HYDATID DISEASE

An increase in antibody content in human sera against sheep erythrocytes has repeatedly been observed in pathological conditions. Thus, Hanganutziu[31], in examining the blood of individuals receiving horse serum parenterally, found agglutinins, not only for sheep cells, but for those of horses, guinea pigs, calves and pigs. This occurs independent of the serum-sickness that may be produced in these individuals. Deicher[10] and Davidsohn[9] stated that these antibodies attain highest concentration in patients with serum sickness. Schiff[53] established that these heterophile antibodies appear also in serum-sickness produced after the injection of therapeutic rabbit serum. Increase in the titre of heterophile antibodies has been found in the serum with infectious mononucleosis[44], in the serum of allergic patients[55] and in some patients who have received injections of liver extracts.

I have found[20,21] that a marked increase of agglutinins and hemolysins against sheep erythrocytes follows the repeated injections of hydatid fluid in some subjects with hydatid cysts. An increase of agglutinins for red cells of other animals, as well as for human red cells, types A and B, can be observed in certain patients who react most intensely to the intracutaneous injection of the hydatid fluid and are not observed in subjects with negative intradermal reaction, in subjects without hydatid cysts or in non-infected rabbits. I presented the hypothesis that for the appearance of this type of heterophilic antibodies previous sensitization of the tissues to the hydatid antigen is necessary. On the other hand, I found that an increase of similar heterophilic antibodies and eosinophiles[26] is produced in patients with positive skin reactions to *Ascaris lumbricoides suum* when these patients are repeatedly injected by the intradermal route with a saline extract of this parasite. The injections of the same parasitic extract in persons with negative ascaris skin reactions or in rabbits do not produce an increase of heterophile antibodies.

In summary, in some patients with positive skin reactions to hydatid fluid, a triple reaction can appear after repeated injections of this antigen: (a) hematological increase of blood eosinophiles, (b) heterophile serological reaction, increase of agglutinins and hemolysins against sheep red cells, (c) a rapid appearance of specific complement fixation antibodies. Unfortunately, the three reactions are not regularly produced, and, therefore, have a very limited diagnostic value.

CLINICAL HYDATID ALLERGY

Typical crises of asthma due to the presence of a hydatid cyst in the liver or in the lung have repeatedly been observed.[2,40] Urticaria, angioneurotic edema and gall-bladder colics are sometimes present in patients who harbor hydatid cysts in the liver. Its possible allergic origin is shown by the beneficial effects of the extirpation of the cyst or desensitization with hydatid fluid.[20,24] In some of these patients we found an increase in

blood histamine[28], but in most patients with hydatid cyst, blood histamine is normal or sometimes subnormal. In man, accidents produced by the rupture of hydatid cysts have been reported in several instances.[13,38] In general, all the symptoms described for human anaphylactic shock are reproduced: deep fall of blood pressure, tachycardia, nausea, vomiting, diarrhea, angioneurotic edema, giant urticaria, et cetera.[7,13] These symptoms are usually attributed to the phenomena of sensitization to foreign antigens present in hydatid cysts. The rupture of the cysts would bring the system into contact with massive doses of substances, to which the organism had been progressively sensitized and anaphylactic accidents would follow combinations of the antigens with the respective antibodies. This hypothesis, however, might be advantageously enlarged in consideration of the fact that severe to fatal shock develops among normal dogs after a first injection of hydatid fluid. This fluid appears to contain an anaphylactoid substance which is primarily toxic for dogs as shown by previous investigators and confirmed by us.[29,50]

ANAPHYLAXIS-LIKE REACTIONS PRODUCED IN DOGS BY HYDATID FLUID

The toxicity of the fluid of Echinococcus granulosus cysts has been reported repeatedly.[12,19,42,43] In the dog, the symptoms were somewhat similar to those of anaphylactic shock, since there was a fall of arterial blood pressure, leukopenia and incoagulability of the blood. After a first response the dogs become desensitized to further injections of the same substance (tachyphylaxis). I have shown first in collaboration with Recarte and Balea[29] and later with Rocha e Silva[50] that in some of the dogs injected with hydatid fluid there is an increase of the histamine content of the blood, but there is not a parallel relation between the concentration of histamine in the blood and the degree of fall of blood pressure. In some dogs there was a decrease, in some an early increase, and in others a late increase of the concentration of histamine in the blood. From these investigations, the general conclusion was drawn that histamine apparently is not concerned with this type of shock. The same type of shock but more grave is produced by the first injection of extract of *Ascaris lumbricoides suum* in dogs.[51]

In spite of Parisot and Simonin's findings[42,43] that the fresh hydatid fluid is highly toxic for the rabbit, we found that the purified products which are toxic for dogs do not produce symptoms in rabbits.[30] The injection of hydatid fluid produces a striking decrease of histamine in the rabbit blood at the same time that a drastic reduction of platelets is observed. From these experiments, the conclusion was drawn that histamine is more likely to be carried by platelets than by leukocytes in the circulating blood of the rabbit.

REFERENCES

1. Bacigalupo, J.: Subcutáneo-reacción quística. Semana med., 1:1083-1084, 1923.
2. Benhamou, E., Thiodet, and Casonova, J.: L'asthme hydatique. Paris Méd., 107:158-162, 1938.
3. Botteri, J. H.: Über Echinokokkenanaphylaxie. Wien. klin. Wchnschr., 35:473-474, 1922.
4. Botteri, J. H.: Über Echinokokkenanaphylaxie. Ztschr. f. d. ges. exper. Med., 44:774-790, 1925.
5. Botteri, J. H.: Echinokokkenantigen. Klin. Wchnschr., 8:836-839, 1929.
6. Casoni, T.: La diagnosi biologica dell'echinococcosi umana mediante l'intradermoreazione. Folia clin. chim. et micros., 4: Nos. 3, 5 and 16, 1911-1912.
7. Chauffard, Boidin and Laroche: Anaphylaxie hydatique expérimentale. Compt. rend. Soc. de biol., 67:499-501, 1909.
8. Culbertson, J. T., and Rose, H. M.: Further observations on skin reactions to antigens from heterologous cestodes in echinococcus disease. J. Clin. Investigation, 20:249-254, 1941.
9. Davidsohn, I.: Further studies on heterophilic antibodies in serum sickness. J. Immunol., 18:31-49, 1930.
10. Deicher, H.: Production of heterospecific hemagglutinins by injection of heterogenous serum. Ztschr. f. Hyg. u. Infectionskrankh., 106: 561-579, 1926.
11. Dennis, E. W.: Stable purified concentrated antigen for immunological study of hydatid disease. J. Parasitol., 23:62-67, 1937.
12. Dessy, S., and Marotta, R. A.: Toxicidad del líquido del quiste hidático. Rev. Soc. med. arg., 20:373, 1912.
13. Dew, H. R.: Hydatid disease; its pathology, diagnosis and treatment. p. 426. Sidney. The Australasian Medical Publishing Company, Ltd., 1928.
14. Fairley, K. D.: Intradermal tests in hydatid disease; critical analysis of its results. M. J. Australia, 1:472-483, 1929.
15. Fairley, K. D., Fairley, N. H., and Williams, F. E.: Some fallacies in the intradermal tests for hydatid disease. M. J. Australia, 2:320-333, 1929.
16. Fairley, N. H.: Researches on the complement reaction in hydatid disease. Quarter. J. Med., 15:244-267, 1922.
17. Fernandez, Ithurrat, E. M., and Calcagno, B. N.: Reacciones biologicas de la hidatidosis. Semana med., 2:864-869, 1922.
18. Ghedini: Recerche sul siero di sangue. Gazz. d. osp., 27:1616, 1906, and 28:53, 1907.
19. Giusti, L., and Hug, E.: Propiétés pharmacodynamiques du liquide hydatique. Compt. rend. Soc. de biol., 88:344-346, 1923.
20. Graña, A.: El tratamiento biológico de la hidatidosis; su acción sobre algunas manifestaciones de alergia hidatídica y las modificaciones serológicas que produce. Día méd., Buenos Aires, 14:1092-1096, 1942.
21. Graña, A.: Antibodies against sheep erythrocytes produced by the injection of hydatid liquid in patients with hydatid cyst. J. Immunol., 48:203-211, 1944.
22. Graña, A.: Anticuerpos heterófilos clinica e inmunologia. p. 54. Buenos Aires: Espasa Calpe, 1944.
23. Graña, A.: Eosinofilias producidas en pacientes con quiste hidatídico injectados con liquido hidatídico. Medicina, Buenos Aires, 4:290-295, 1944.
24. Graña, A.: Tratamiento biológico de la hidatidosis; su acción sobre algunas manifestaciones de alergia hidatídica. Prensa méd. argent., 31:733-737, 1944.
25. Graña, A.: Alergia y diagnostico biológico de la hidatidosis. Arch. urug. de med., cir. y. especialid, 26:538-559, 1945.
26. Graña, A.: Antibodies against sheep erythrocites and eosinophiles produced in subjects injected with saline extract of *"Ascaris lumbricoides suum."* Rev. brasil. de biol., 5:81-86, 1945.
27. Graña, A.: Titulo de isoaglutininas en patients con quiste hidatídico injectados con liquido hidatídico. Medicina, Buenos Aires, 5:365-368, 1945.
28. Graña, A., Recarte, P., and Balea, E.: La histaminemia en la alergia hidatídica. Medicina, Buenos Aires, 3:198-201, 1943.
29. Graña, A., Recarte, P., and Balea, E.: La histaminemia en la choque producido por el liquido hidático en el perro. Rev. soc. argent. de biol., 19:444-446, 1943.
30. Graña, A., and Rocha e Silva, M.: Effect of hydatid fluid on histamine content of rabbit blood. Am. J. Physiol., 143:314-323, 1945.
31. Hanganutziu, M.: Hémagglutinines hétérogénétiques aprés injection de serum de cheval. Compt. rend. Soc. de biol., 91:1457-1459, 1924.
32. Imaz Apphatie, I. L., and Lorentz, E. Rev. Soc. med. argent., 16:625, 1908.

33. Kellaway, C. H.: Diagnosis of hydatid disease; Casoni reaction. M. J. Australia, 1:436-437, 1925.
34. Kellaway, C. H.: Utility of the Casoni reaction in the diagnosis of hydatid disease. M. J. Australia, 1:417-418, 1925.
35. Kellaway, C. H.: The diagnosis and surgical aspects of hydatid disease. M. J. Australia, 1:479-480, 1927.
36. Kellaway, C. H.: Hydatid fluid as anaphylactic antigen. J. Path. & Bact., 31: 141-156, 1928.
37. Kellaway, C. H., and Fairley, K. D.: Clinical significance of laboratory tests in the diagnosis of hydatid disease. M. J. Australia, 1:340-342, 1932.
38. Lozano, R.: Chascos y peligros de la hidatidosis; el "shock" anafiláctico mortal. Arch. internac. de la hidat., 1:95-99, 1934.
39. Mollow, W.: Die bedeutung der Reaktion nach Casoni fur die diagnosis der Echinokokkenkrankheit der Menschen und ihre Einwirkung auf die anderen biologischen Reaktionen. The Cairo II° Congress. Int. Med. Hyg. Trop., p. 649, 1928, and Arch. f. Schiffs. u. Tropen. Hyg., 32:187-194, 1928.
40. Mussio Fournier, J. C., and Seoane, C.: Asthme, oedème de quincke et quiste hydatique du foie. Bull. et mém. Soc. med. d. hôp. de Paris, 51:327-329, 1927.
41. Outeirino, J.: Recherches sur la prétendue spécificité des réactions de Ghedini-Weinberg et de Casoni dans le diagnostic de l'échinococcose humaine. Ann. de méd., 38:493-509, 1935.
42. Parisot, J., and Simonin, P.: Action du liquide hydatique sur les appareils circulatoire et respiratoire. Compt. rend. Soc. de biol., 83:149-151, 1920.
43. Parisot, J., and Simonin, P.: Recherche sur la toxicité du liquid hydatique Compt. rend. Soc. de biol., 83:74-76, 1920.
44. Paul, J. R., and Bunnell, W. W.: Presence of heterophile antibodies in infectious mononucleosis. Am. J. M. Sc., 183:90-104, 1932.
45. Pinelli, L.: La diagnosi biologica dell echinococcosi. Arch. internac. de la hidat., 2:75-127, 1936.
46. Pirosky, I., Pirosky, R., de, and Casiraghi, J. C.: Hipersensibilidad de infestación en la hidatidosis del hombre. Rev. d. Inst. bact., Buenos Aires, 11:94-98, 1942.
47. Pirosky, I., Pirosky, R., de, and Francischi, C.: Polisacárido aislado de quiste hidático. Rev. d. Inst. bact., Buenos Aires, 10:230-232, 1941.
48. Pontano, F.: Intradermo e Sottocutaneoreazione con liquido cistico nelle echinococcosi umana. Policlinico (sez. med.), 27:405-421, 1920.
49. Rachemann, F. M., and Stevens, H. A.: Skin tests to extracts of echinococcus and ascaris. J. Immunol., 13:389-390, 1927.
50. Rocha e Silva, M., and Graña, A.: Shock produced in dogs by hydatid fluid. Am. J. Physiol., 143:306-313, 1945.
51. Rocha e Silva, M., and Graña, A.: Anaphylaxis-like reactions produced in dogs by ascaris extracts. Arch. Surg., (in press).
52. Rosello, H.: Sur l'eosinophilie hydatique. Compt. rend. Soc. de biol., 63:423-425, 1907.
53. Schiff, F.: Heterogenetic hemagglutinins in man following therapeutic injections of immune sera produced in rabbits. J. Immunol., 33:305-313, 1937.
54. Senekji, H. A.: Polysaccharide scolex antigen for immunological diagnosis of hydatid disease. Tr. Roy. Soc. Trop. Med. & Hyg., 34:401-403, 1941.
55. Sinclair, M. W., and Thomas, J. W.: Heterophilic antibody determinations in 148 allergic and 107 nonallergic persons. J. Allergy, 10:228-234, 1939.
56. Tanturi, C. A.: Los eosinófilos de la hidatidosis. Semana med., p. 2, 1493, 1650, 1698, 1939.
57. Testi, A., and Zoli, C.: Echinococcus intradermal reactions. Riv. di clin. med., Florence, 20: No. 51, 601, 1919. Abst. J.A.M.A., 1133, 1920.
58. Urioste, J. P., and Scaltritti, A.: Contribution a l'etude de l'echinococcose. Presse méd., 1: No. 7, pp. 47-59, 1911.
59. Weinberg, M.: Sero-diagnostic de l'echinococcose. Ann. Inst. Pasteur, Paris, 23:472, 1909.
60. Weinberg, M., and Parvu, M.: Reaction de Bordet Gengou dans les helminthiasis. Compt. rend. Soc. de biol. Paris, 55:298-300, 1908.

ASTHMA DUE TO BEE SCENT

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IT is not uncommon for individuals to show varying degrees of hypersensitivity to insect bites, wing scales, bodies of insects, the injection of venom or the introduction of salivary secretions.[2,3,4,5]

According to Ellis and Ahrens[1] any reference to hypersensitiveness to air borne allergens of bee origin could not be found in the literature. They report two cases in which asthma was initiated when near bees or objects that had been in contact with bees. Skin tests were positive to pollens from hives, honey, whole bee, bee abdomen, thorax, head, and other parts of the bee, but found a negative reaction to bee wings.

The following case will, I believe, be of interest because it shows that a patient may be sensitive to the scent of the bee and this scent which is heavy may cling to various parts of the bee body components of the hive and to any substance in which it may come in contact and so cause asthma.

The idea of scent-producing organs in bees was proposed by Sladen (1901). Nassonoff first described these glands in 1883. Snodgrass[6] says that Sladen, pointing out that bees were not known to have a sense of hearing suggested that the "joyful hum" of bees around the hive served as a signal and guide to the other bees. He believed that the sound is merely incidental to a fanning of the wings made to drive the scent away from the body, and that, not the sound, but "the scent produced forms a means of communication between the members of a swarm or colony."

Snodgrass continues: "This view concerning the function of the glands of Nassonoff is now generally accepted, and has recently been much elaborated by von Frisch (1923), who includes the abdominal scent as one of the important elements in the 'speech' of bees. He observes that a bee gathering nectar from flowers or drinking sugar water from a dish set out in the apiary flies about the place with the end of the abdomen protruded, and also exposes the outlets of the scent glands while drinking. In this way she marks the position of the food source with her odor, and the other bees, told of its existence by the customary dance of the returning bee in the hive, are then able to find it for itself in the field."

The patient, S. O. H., male, aged forty-one, provincial apiarist, consulted me first in 1938 with a history of asthma when anywhere near bees or on opening a small container with even a few dead bees sent for examination.

He gave no history of any other personal or family allergy. He was immune to bee venom, on one occasion he had over 200 stings and the only symptom was drowziness. To this might be added the fact that he developed immunity to venom early in his career. Here follows his essential history in this condition as written at that time by himself.

"I began working with bees about seventeen years ago and had no disagreeable symptoms of any kind until eight years ago. At that time, while working in large apiaries near Lethbridge, I noticed an almost unbearable itching under the chin, and later on, an itching in the corners of the eyes. This occurred during the first two weeks of September, then, the bee season being over, I gave no further thought to the matter. As soon as I left the yards and washed my face and hands the symptoms I speak of disappeared.

"The following year the same symptoms occurred during the latter part of August and continued until the end of the bee season. They were more pronounced and the itching, especially in the corners of the eyes, would be there for several hours after leaving the yards. Three years after my first symptoms occurred I had symptoms which I considered to be hay fever. The itching under the chin disappeared. The itching in the eyes became more intense and they continued to water—there were frequent discharges of a watery mucous from my nose. Again these symptoms appeared about two weeks earlier than they had in the previous year. At this time I also had some evidence of very slight sinus headaches, but not serious.

"About four years ago I began to have difficulty in getting my breath from June on, and found it difficult to sleep. Usually, I sat in a chair until around 12:00 or 1:00 o'clock after working in a large apiary and then slept very soundly until the morning. There was no change in the intensity of the symptoms—though they seemed to appear a little earlier each year until last spring.

"Last spring the symptoms of what I thought to be hay fever attacked me when I examined my first yard, watery mucous discharges from the nose were pronounced, and breathing was difficult in the yards. In previous years I had noticed no difficulty in breathing until I went to bed. The symptoms became more and more severe throughout the summer, though I was handling fewer colonies than usual—and a pronounced lassitude, which gradually increased to grave weakness, grew on me through the summer. By August, I found that I could not sleep and rarely took dinner at night. Usually, I went home to bed, propped myself up with four or five pillows and tried to rest. I suffered from nausea throughout the evening and found no relief until 2:00 or 3:00 o'clock in the morning, when vomiting occurred. I would then sleep. During August I had such pronounced pain in my left lung that I consulted a physician, thinking I had pleurisy. He told me that it was a textbook case of allergy and advised me to resign from my position as Provincial Apiarist and get away from bee-keeping entirely."

In view of his history, tests were made of all the common pollens which cause pollinosis in this region with negative results.

Extracts were made from the various parts of bees with a buffer solution and tests done by the intracutaneous method. Positive reactions to all parts including the wings were markedly positive. Passive transfer was successfully carried out. A small part of a bee's wing was placed in the external angle of one eye and in less than one minute the whole eye was injected; one wing placed in the nostril caused sneezing and lachrymation.

Since the wings of the bee are composed of almost pure chitin, extracts were made of the wings of other insects composed of chitin with no positive reactions.

The patient suggested that possibly the scent was responsible for the asthma. In order to find if this was so, the bee wings were washed well with acetone before making a new extract. The test was negative. Next the scent glands were dissected out and the contents of one gland was placed in buffer solution. The skin reaction was now a marked positive.

The scent from one gland was placed in a small vial of ether. Three other vials of ether were prepared. The patient was unaware which vial contained the scent. He was given two vials of ether to inhale in succession with no effect. The third vial which contained the scent when inhaled caused an attack of asthma within one minute. The condition was severe enough to require adrenalin to control it.

Since it seemed unlikely that the patient would be able to carry on his occupation with bees he was anxious to engage in entomology. To find if other insects would cause his asthma extracts of over one hundred of these related to the bees were prepared and intracutaneous tests were carried out.

These included the Orthoptera, Hemiptera, Coleoptera, and Diptera particularly. Delayed reactions to a few members of the Coleoptera or water beetles were obtained. As some members of this subfamily possess rectal glands which excrete volatile offensive gaseous or liquid substances, it is possible that these reactions were due to these and of an irritant nature.

SUMMARY

A case is reported in which a patient suffered from asthma from the scent of the bee. He gave skin reactions to all members of the superfamily of the Apoidea, but to no other member of the superfamily of Hymenoptera. Asthma resulted from inhalation of bee scent glands dissolved in ether. Positive skin reactions were obtained from an extract of bee wings. Passive transfer was carried out. An extract of bee wings washed with acetone gave negative skin reactions.

REFERENCES

1. Ellis, R. V., and Ahrens, H. G.: Hypersensitiveness to air borne bee allergen. J. Allergy, 3:247, (March) 1932.
2. Figley, K. D.: Asthma due to the May fly. Am. J. M. Sc., 178-338, (Sept.) 1929.
3. Jamieson, H. C.: The house fly as a cause of nasal allergy. Am. J. M. Sc., 9:273, (March) 1938.
4. Parlato, S. J.: A case of coryza and asthma due to sand flies (Caddis flies). J. Allergy, 1:35, (Nov.) 1929.
5. Parlato, S. J.: The sand fly (Caddis fly) as an exciting cause of allergic coryza and asthma. J. Allergy, 1:307, (May) 1930.
6. Snodgrass, R. E.: Anatomy and Physiology of the Honeybee. New York: McGraw Hill Book Co., Inc., 1925.

A METHOD OF OBSERVING TRANSIENT LEUKOPENIA. Essex, H. E., M.D., and Grãna, A. (By invitation), Mayo Foundation, Rochester, Minnesota. Federation Proceedings, Part II, 5:25, February, 1946.

By means of a transparent chamber (Clark, Florey) inserted in the ears of rabbits, the authors observed the leukocytic behavior in newly formed blood vessels following intravenous injections of certain amounts of glycogen, gum acacia, extracts of *Ascaris Suum* and hydatid cyst fluid. These injections were followed by a majority of the leukocytes adhering to the walls of the veins in one or two minutes and ceasing to move. The leukocytes were observed to adhere to the vessel walls and to each other, forming small clumps. In 15 to 30 minutes the cells usually separated from each other and the vessel walls, and again entered the circulation. During that period of their vessel adherence, there was a consequently marked leukopenia in the blood obtained from the ear or leg vein. The lowest leukocyte counts corresponded with the period of altered behavior when the cells were adherent to the walls of the veins.

Their observations suggest to the authors that the reaction is a general one. They also noted that the behavior of the leukocytes was not influenced by injections of glucose or a serum or physiologic salt solution.

The authors are continuing their observations by noticing the behavior of the leukocytes following the injection of other substances as well as that following anaphylactic shock, in order to determine whether a chronic leukopenia can be produced by the prolonged administration of certain substances.

HEADACHES

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MIGRAINE has been defined as paroxysmal attacks of hemicrania (occasionally bilateral headaches), which are associated with sensory and motor disturbances. These latter disorders, effecting vasomotor changes, crossed hemicrania, hemianopsia, unilateral paresthesias, and the like, point toward an involvement of the cerebral cortex itself.[1]

Migraine is commonly considered a one-sided headache usually with an aura, with nausea and vomiting, vertigo, lethargy, frequent photophobia, and terminating in a relief as sudden and unexplained as its onset. In this present study, migrainous headaches with one or more of the usual prodromata were found to be unilateral, generalized, and, in 3 per cent, unilateral and generalized on different occasions in the same individual. In an effort to include only migraine, the term *tension headaches* was used in this series until a definite link could be made between the unilateral and the more generalized headaches. Comparison later established them to be of the same etiological factor, the principal point of variance being their distribution.

Headaches associated with nasal blockage and obvious Horton's syndrome cases were excluded from this study. The aurae that this group experienced varied from a sudden oppressive fatigue to olfactory, visual, and auditory ones. Eighty-seven per cent of the patients in this series at one or more times had received ergotamine tartrate at the onset of an attack not only for relief but also to serve as a further diagnostic aid.

In 1927 Vaughan demonstrated that food sensitivity could be responsible for migraine.[13] Others have confirmed this fact.[5,12]

This malady has also been studied extensively from the standpoint of endocrine involvement. Mazer and Israel conclude that some migraine is caused by an allergy to the follicle-stimulating hormone which could be suppressed by adequate estrogen therapy. They failed to give relief by estrogen therapy in only five out of thirty-four patients designated as "the menstrual type."[9] Another opinion describes an imbalance in the anterior pituitary-ovarian relationship with hyperfunction of the pituitary and hypofunction of the ovaries in migraine production.[11] Hoffman cites Goldzieher's opinion by explaining migraine as an outcome of increased water and salt retention in the tissues preceding menstruation. Adding to this an increased nervous instability and an increased capillary permeability which normally precede menstruation, there is an increase in intracranial pressure resulting in pain. The increased intracranial pressure was thought to stimulate anterior hypophyseal function causing an elaboration of more gonadotrophic hormone.[7]

Psychologically the migraine sufferer has been described as one socially and emotionally maladjusted, with psychoneurotic, but not psychotic,

trends in the personality.[10] The possibility of a disturbed sympathetic innervation with resulting vasomotor changes has also been suggested in regard to production of migraine.[15] Shyness, rigidness of personality, perfectionism, extreme sensitiveness, sex maladjustment, abnormal attachment to a parent, emotional tension, anxiety, driving ambition, and other factors have been offered as the psychobiologic aspect of migraine sufferers.[16]

It would seem that the main factors to be considered in the proper evaluation of the mechanism producing migraine as well as its treatment are allergic, endocrinological, and psychic in nature. The common denominator of migraine or tension headaches is a cerebral edema produced by a primary vasomotor spasm followed by a secondary vascular dilatation.[8] Increased intracranial pressure has been reported to be present during the attack and is eventually equalized with its termination.[6] The variety and difference in pain distribution, as well as aura experienced, can be explained on the basis of the part of the brain involved and whether the edema be localized or generalized[2,4,14]; and also by distention of the cranial arteries involved.[3]

In this series of one hundred migraine or tension headaches, sixty-three were female and thirty-seven male. Each was studied from the allergic, glandular, and physiological viewpoints. Consultations with gynecologists, endocrinologists, psychiatrists, neurologists, and allergists were obtained in all doubtful cases.

The emotional factor embodied the psychoneurotic pattern and at no time was a frankly psychotic or mentally defective individual uncovered.

Diagnoses of glandular deficiencies were made after careful history, physical examination, laboratory, x-ray, smear and tissue studies had been done. Only one case, and that of a male, showed a glandular (gonadal) hyperfunction.

The allergic familial history was considered contributory if migraine, "sick, one-sided headaches," bronchial asthma, hay fever, or eczema were found to have existed. If, in addition to migraine, the patients had one or more allergic conditions such as hay fever, eczema, and the like, this was thought important enough to record in favor of an allergic factor.

The entire group was tested completely to foods and the gastro-intestinal factor was not considered salient unless at least ten or more strong (4+) reactions were obtained. Tests were made by scratch, then endermal methods. This was followed by endermal retesting. In some cases, diet elimination studies with carefully recorded food charts were required. In the earlier cases, leukopenic indices and blood enzymic studies were carried out but later omitted because of unreliable results obtained.

In order to clarify better the problem of physical allergy in those who complained of precipitation of headaches when exposed to drafts, the incidence of dust sensitivity was included along with the thermal factor.

TABLE I. FACTORS IN REGARD TO HEADACHES

	Generalized (46)	Unilateral (51)	Entire Group (100)
1. Emotional	50%	59%	54%
2. Glandular Deficiencies			
(a) Pituitary	15%	19%	18%
(b) Thyroid	34.7%	35%	35%
(c) Gonadal	39%	49%	38%
3. Hypergonadal	2.1%	0%	1%
4. With Allergic Familial History	39%	36%	36%
5. With Concomitant Allergy	43%	46%	46%
6. With Food Allergy	63%	82%	73%
7. With Inhalant Allergy	34.7%	56%	48%
8. With Thermal Allergy	36.9%	36%	38%
9. With Marked (4 +) Dust Allergy	28%	24%	26%
10. Type Headache			
(a) Right unilateral			22%
(b) Left unilateral			33%
(c) Total (left and right unilateral)			55%
(d) Generalized			46%
(e) Both			3%

Only marked (4+) dust sensitivities were included in this study.

Over half of the entire group had unilateral headache with a psychoneurotic predisposition, but the most important factor is the gastrointestinal allergic one. Next in importance to food and emotional factors comes inhalant allergy. That the allergic factor is the most important one is substantiated by the high incidence of the allergic hereditary factor and the presence of other allergic manifestations in the individual. The majority manifested sensitivity to temperature changes alone rather than to dust.

Gonadal and thyroid deficiencies were the prominent glandular abnormalities found. Pituitary deficiencies in this series proved practically negligible. Only one case of hypergonadism was seen.

Whether the headaches manifested were unilateral or generalized, the factors for the entire group remained fairly constant; however, in unilateral headache there was the greatest incidence of food allergy, emotional instability, and inhalant allergy in the order named (Table I).

The principal sensitivities to foods in the majority of cases were cereals (predominantly wheat), the legumes, seafoods, and cow's milk.

Treatment consisted of diet elimination, pollen desensitizations, gonadal substitution therapy, and thyroid when indicated. The patients, with the exception of two, were able to overcome their conflicts without aid of a psychiatrist.

All patients remained free of migraine so long as absolute avoidance of the offending foods was observed and so long as the emotional factor was controlled.

Thermal allergy was treated by contrast baths. The degree of favora-

ble response to this method alone cannot be ascertained, in that other desensitizations were being simultaneously employed.

Migraine, because of its predominant allergic basis, should be handled by the allergist, who must be constantly aware of the psychoneurotic element in over half of the migraine sufferers he sees. This important psychological aspect of the problem, along with indicated glandular therapy, and necessary allergic desensitization, offers the best chance of recovery.

The term "tension headaches" can be discarded. Enough common factors have been established, regardless of headache distribution, to warrant the entire series to be called migraine headaches.

Ten per cent of the patients have had recurrence of migraine while on treatment. In most cases the attack was traced to a dietary violation. A minority of this group of recurrent headaches precipitated the migraine by an emotional conflict.

SUMMARY

1. Migraine, whether unilateral or generalized, is explained on a basis of localized or generalized cerebral edema with resulting increased intracranial pressure.

2. Listed in order of their importance are factors to be considered in the proper management of migraine sufferers: food sensitivity, the psychological aspect, inhalant sensitivity, physical allergy, and glandular deficiencies.

BIBLIOGRAPHY

1. Balyeat, R. M.: Allergic Diseases, Their Diagnosis and Treatment. Philadelphia: F. A. Davis Company, 1938.
2. Clark, T. W.: Allergic manifestations in the central nervous system. New York State J. Med., 39:1498, 1939.
3. Clarke, T. W.: Allergy of the central nervous system. Ann. Allergy, 2:189-196, (May-June) 1944.
4. Criep, L. H.: Allergic vertigo. Pennsylvania M. J., 43:258, 1939.
5. Crowe, W. R.: Cerebral allergic edema. J. Allergy, 13:173-176, (Jan.) 1942.
6. Goltman, A. M.: The mechanism of migraine. J. Allergy, 7:351, 1936.
7. Hoffman, J.: Female Endocrinology. Philadelphia: W. B. Saunders Company, 1944.
8. Kennedy, F., Wortis, S. B., and Wortis, H.: Clinical evidence for cerebral vasomotor changes. New York State J. Med., 38:1441, 1938.
9. Mazer, C., and Israel, S. L.: Menstrual Disorders and Sterility. New York-London: Paul B. Hoeber, Inc., 1941.
10. Moore, M., Gray, M. J., et al.: Personality of patients with migraine. J. Nerv. & Ment. Disorders, 97:509-517, (May) 1943.
11. Riley, H. A., Bricknew, R. M., and Kurzrok, R.: Abnormal excretion of theelin and prolan in patients suffering from migraine; Preliminary report. Bull. Neurol. Inst., New York, 3:53, 1933.
12. Thomas, J. W., and Johnston, C. R. K.: Headaches of allergic origin. M. Clin. North America, 24:285, 1940.
13. Vaughan, W. T.: Allergic migraine. J.A.M.A., 83:1383, 1927.
14. Vaughan, W. T.: Practice of Allergy. St. Louis: C. V. Mosby Company, 1939.
15. Wechsler, I. S.: A Text Book of Clinical Neurology. Philadelphia and London: W. B. Saunders Company, 1932.
16. Wolff, H. J.: Personality features and reactions of subjects with migraine. Arch. Neurol. & Psych., 37:895, 1937.

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SEDIMENTATION RATE—A DIAGNOSTIC AID IN ALLERGY

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IN searching for additional aids in differential diagnosis of allergic and non-allergic diseases, a record was kept of 3,000 sedimentation rates in the past year. These readings covered many different diseases. An attempt has been made to use these readings in an effort, if possible, to avoid unnecessary allergy diagnostic procedures. These observations seem to explain part of our past failures, since it appears many symptoms were not due to allergic exacerbations.

The sedimentation tests were made with a Landau-Adams apparatus, and results were noted at the end of one hour. When possible, observations were made on each patient throughout the year. Frequent observations were made in seasonal cases during their seasonal increase of symptoms. Normal readings in this apparatus are included in the range from 1 to 10 mm. Infectious diseases have readings well above 25 mm.

Infections and other conditions causing an increase in sedimentation rates are:

1. Pharyngitis, adenoiditis, rhinitis, dental caries, rheumatic fever, endocarditis, chorea, nephritis, complicated tuberculosis, erythema nodosum, salpingitis and other gonorrheal infections, toxic malignancies, syphilis, tonsilitis, endometritis, chancroid, cholecystitis, rectal abscess.
2. Blood dyscrasias as leukemia, purpura, polycythemia vera, pernicious anemia, et cetera.
3. Pregnancy and tubal pregnancy.
4. After use of x-ray or radium therapy—gelatine.
5. Vascular lesions.

Conditions which inhibit the sedimentation rate are: jaundice (if the bile acid is increased in the blood), alcohol, novasural, sodium salicylate and quinine.

RESULTS

1. *Allergic Migraine.*—Nine cases. All had readings between 2 and 8 mm. in one hour, except two. One had cholecystitis and colitis, and the

Suggestions or articles intended for this department should be submitted to Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas.

rate dropped from 40 to 10 mm. when these factors were eradicated. One had a reading of 17 mm. which went down to 10 mm. when her sinusitis subsided.

2. *Histaminic Cephalalgia.*—Three cases. All readings 3 to 4 mm. in one hour.

3. *Bronchial Asthma.*—Forty-five cases of uncomplicated bronchial asthma had readings between 3 and 10 mm.

4. *Hay Fever.*—Thirty-two cases. All had sedimentation readings between 1 and 10 mm. in one hour. Pollen in the air had no bearing on their readings.

5. *Allergic Rhinitis.*—Sixty-five cases. All had readings from 1 to 10 mm. when controlled under proper management. Ten cases had an increase above 10 mm. either before treatment started or at some time during the year because of other causes. The sedimentation rate returned to normal when infections were cleared.

6. *Hives.*—Six cases of uncomplicated and proven allergic hives had normal readings.

7. *Allergic Bronchitis.*—Nine patients. Seven had normal rates at the start. Two cases had 20 and 26 mm. These became normal as soon as the complicating infection was cleared.

8. *Angioneurotic Edema.*—Five cases of angioneurotic edema which were proven to be of allergic origin had readings from one to ten mm.

9. *Eczema.*—Fifteen cases of eczema had normal readings.

Of the complications that arose in allergic patients, some are listed with their effects on sedimentation rates:

Acute arthritis (two cases)—readings 25 to 45 mm.

Acute gonorrhea (one case)—reading 50 mm.

Influenzal bronchitis (twelve cases)—readings 30 to 45 mm.

Rheumatic fever (two cases)—readings 30 to 40 mm.

The mechanisms by which sedimentation rates are changed are:

(a) Any condition causing an increase in viscosity of the blood causes an increase in sedimentation rate.

(b) Decrease of the albumin in the blood causes an increase in sedimentation rate.

(c) In a tuberculosis patient getting BCG vaccine, the sedimentation rates become normal when the patient develops allergy to the vaccine.

(d) Destruction of tissue by x-ray or by tumors causes absorption of tissue or toxic substances with increased sedimentation rates.

CONCLUSIONS

Sedimentation readings have been an aid in differentiating allergic and non-allergic diseases and have avoided some unnecessary allergic diagnostic procedures. They have also explained some of our failures. Many

former failures have been brought under control by aid of other medical therapy which explains some of the puzzling "flare-ups" in allergic patients. Sedimentation rate observations are done very easily and have a very small percentage of errors (5 per cent). These observations would indicate that routine blood sedimentation observations should be done on allergic patients, since many patients with hypersensitiveness have complicating diseases which are not of an allergic nature. This simple procedure may be a diagnostic aid when differentiating those allergic patients who are suffering from other diseases as well.

REFERENCES

1. Landau, Albin: Micro-sedimentation: Its serviceability and significance to pediatrics. Am. J. Dis. Child., 45:691, 1933.
2. Wunderly, C., and Wuhrmann, F.: Reaction mechanism of erythrocyte sedimentation and plasma model. Schweiz. med. Wchnsch., 74:185, 1944.
3. Matchieu, Albert, Trotman, Frank, Haskins, Howard D., and Albert, Joyce: Sedimentation rate in gynecology and obstetrics. Am. J. Obst. & Gyn., 21: 197, 1931.
4. Wulff, H.: Sedimentation rate after roentgen and radium therapy. Acta radiol., 13:686, 1932.
5. Lippross, C., and Engel, H.: Differential diagnosis and prognostic significance of repeated simultaneous determination of sedimentation rate of erythrocytes. Klin. Wchnschr., 20:453, 1941.
6. Wilder, Gordon B.: Sedimentation rate of red blood cells. J. Indiana M. A., 34:24, 1941.

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Correction.—On Page 139 of the March-April issue of the ANNALS OF ALLERGY there was an error in the formula of the stain. The formula should read:

Eosin, yellowish, alcohol and water soluble	0.5 mg.
Ethyl alcohol	95%/100. c.c.

PENICILLIN DERMATITIS BASED ON TUBERCULIN-TYPE SENSITIVITY

(Continued from Page 195)

injections produced a reaction. The latter was of the delayed so-called tuberculin type. All patch tests with penicillin on skin previously unaffected were negative. The clinical lesions as well as those produced experimentally on a finger of the patient presented the picture of a "dysidrotic" dermatitis. This case is considered as a penicillin dermatitis based on tuberculin-type sensitivity.

Two of four volunteers used as controls in passive transfer became allergically sensitized to penicillin.

REFERENCES

1. Graves, W. N., Carpenter, C. C., and Unangst, R. W.: Recurrent vesicular eruptions appearing during administration of penicillin. Arch. Dermat. & Syph., 50:6, 1944.
2. Pyle, H. D., and Rattner, Herbert: Contact dermatitis from penicillin. J.A.M.A., 125:903, 1944.
3. Rostenberg, A., Jr., and Sulzberger, M. B.: A list of substances for patch testing, and the concentrations to be employed. J. Invest. Dermat., 2:93-117, 1939.
4. Rostenberg, A., Jr., and Welch, H.: A study of the types of hypersensitivity induced by penicillin. Am. J. M. Sc., 210:158-167, 1945.
5. Welch, H., and Rostenberg, A., Jr.: A case of hypersensitivity of the tuberculin type to crystalline penicillin sodium. J.A.M.A., 126:10, 1944.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *are individual and do not necessarily represent the group opinion of the Board or of the College.*

BACTERIAL ALLERGY

The allergist is used to dealing with non-viable and *per se* non-toxic antigens. Therefore, it is not surprising that he sometimes finds it difficult to adapt himself to the complications that necessarily arise if the *causa peccans* is viable and (sometimes) poisonous. It is obvious that an antigen that is viable and not indifferent *per se* must greatly complicate both the clinical picture and the considerations dominating its analysis. As a matter of fact, for what is commonly understood by the term "allergic diseases," there is so little clear-cut evidence of supersensitivity to micro-organisms that the clinician is greatly tempted to simplify his position by denying the existence of what cannot be reduced to simple facts.

Psychologically his attitude is quite understandable. However, a number of micro-organisms—and the term is used deliberately because it includes viruses as well as bacteria—are antigenic. For almost any of those which have been more closely investigated, antigenicity has been found for more than one component such as proteins, carbohydrates and lipids. And furthermore, it is a fact that the host may become supersensitive to such substances, a piece of knowledge put to use every time we make a tuberculin test. Thus, at least for tuberculosis, the occurrence of supersensitivity has become so trite that it is not often associated any more with the common ground on which our information both on tuberculin supersensitivity and on allergic diseases has grown.

Moreover, the physician knows of the accelerated reaction after repeated innoculations, say of vaccinia virus. He accepts the fact that scarlet fever represents a supersensitivity to a streptococcus that in itself is not very toxic. He has learned, even though he does not usually employ it, that an infection rather regularly leaves demonstrable signs of reactivity to microbial substances as, for instance, pneumococcal carbohydrate. Most of these phenomena do not fall neatly into the pattern we are accustomed to see in allergic diseases. But they all represent the basic phenomena of highly and occasionally catastrophically (tuberculin!) increased and accelerated reaction. Thus, it appears that the general practitioner may be able to give a point to his specialized colleague.

Of course, the allergist may reply that this is all perfectly true and correct, but that is none of his concern because he is not dealing with

infectious diseases. Thus, the question comes up whether he is or is not. The answer depends on what one calls infection. It is certainly "no," if the term is restricted to epidemic diseases. However, the outer and inner surfaces of the human body are covered with micro-organisms. Most of them are harmless enough commensals, others are conditionally pathogenic, as for instance, the flora of our throat, and occasionally there is a powerful killer which is just waiting for a port of entry. The allergist will agree that the integument of every human being is somewhere penetrated every day by micro-organisms which are immediately dealt with by the usual defense mechanisms without leaving any record worthy of medical attention. Still one should think that these contacts are bound to be intensive enough to impress the mechanism that leads to antibody response, and indeed we have evidence that that is the case. Also, there is the problem of intestinal absorption of bacterial antigens. (The counterpart for yeasts and molds is positively known, as for instance, in the cases that tolerate milk but not cheese).

It would be more natural to wonder why such continuous antigenic stimulus does not lead more frequently to striking and easily recognizable allergic reactions than to doubt that microbial sensitization does occur. One may make the conjecture that in continuous intermittent contact, immunity phenomena dominate the picture, just as we are often able to overcome pollen allergy by perennial immunization. From this point of view one may wonder whether the familiar disposition to trivial infections noted, for instance, by Locke and Coca may not be based on a disturbance of the normal balance between sensitization and immunity, in favor of the former in individuals particularly prone to allergic reaction and/or underendowed in their immunity apparatus.

In any case, there is no basic reason why persons of the necessary constitutional make-up should not react vehemently to bacterial antigens. In the case of certain types of asthma, this is quite widely and naïvely accepted to be the case. The scientifically minded among us will say: "quite possible but where is the proof?" Indeed, there is no proof. However, the point is that there is no proof not because there is nothing to be proved but because we really have made no systematic effort to prove or disprove. As to these things we are actually still in a position comparable to that in which we were at a time when people knew quite well they would get hay fever attacks when they went for a walk through a meadow, but nobody knew what that meadow did to those people to make them weep. The meadow contains many things, and it took some doing before we found which of the many things was the causative agent. Our inner and outer body surfaces harbor a great variety of micro-organisms and it will take some doing to find out whether, for instance, bacterial antigens may make an asthmatic wheeze—as conjectured—and, if so, in what cases and under what conditions. The

allergists started by asking the botanist what grows on that meadow, and then they put to use what they had learned. The allergists will have to go to the bacteriologist in order to find out about our microbial guests, and then they will have to apply what they have learned. For instance, they will learn to take into consideration the great variety of microbia involved and they will discover that it is not enough to know that a certain species is present. They may have to apply what the bacteriologist has found out about the immunological types of these species because that is what determines the immunity reactions and would therefore be expected to dominate the specificity of allergic reactions. To return once more to the example of the meadow: It obviously would have been wrong if the search for the agent causing hay fever had been restricted to poisonous plants. From what has been said before, it ought to be just as obvious that the investigation of the problem of the relations between microbial substances and allergy should not be restricted to pathogens and particularly to organisms of high pathogenicity. Commensals may be as important as the known pathogens.

It looks like a big order, and it is one. But only by putting to use the painstaking methods of modern bacteriology we will be able to replace notions by exact information. And this information will be necessary before we can state with any degree of confidence whether or not microbial antigens are involved in a given manifestation of allergy. Maybe a few years hence we shall be able to talk less about conjectures and more about facts. A.J.W.

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two cases. Arch. Dermat. & Syph., 50:320-326, (Nov.) 1944.
3. Brown, E. A.: Drugs. A review of the literature for 1944. Ann. Allergy, 3:216, (May-June) 1945.
4. Criep, L. H.: Allergy to penicillin. J.A.M.A., 126:429-430, (Oct. 14) 1944.
5. Freyhan, F. A.: Pruritus, a side-effect of the penicillin therapy. Delaware M. J., 16:177-179, (Nov.) 1944.
6. Keefer, C. S.: Penicillin—Its present status in the treatment of infections. Am. J. M. Sc., 210:147, (Aug.) 1945.
7. Keefer, C. S., et al.: Penicillin in the treatment of infections. J.A.M.A., 122: 1217, (Aug. 28) 1943.
8. Lyons, C.: Penicillin therapy of surgical infections in the U. S. Army. J.A.M.A., 123:1007, (Dec. 18) 1943.
9. Pyle, H. D., and Rattner, H.: Contact dermatitis from penicillin. J.A.M.A., 125:903, (July 29) 1944.
10. Rotenberg, A., Jr., and Welch, H.: A study of the types of hypersensitivity induced by penicillin. Am. J. M. Sc., 210:158, (Aug.) 1945.
11. Silvers, S. H.: Contact dermatitis from amorphous sodium penicillin. Arch. Dermat. & Syph., 50:328-329, (Nov.) 1944.

Progress in Allergy

THE HOUSE DUST ANTIGEN
A Critical Review of the Literature

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THE present historical review lists the more important contributions to the problem of the house dust antigen and its relation to respiratory tract allergy. It was hoped that by reviewing the data published since Kern's first paper in 1921[43], a more definite direction might be given to future experimental and clinical investigation in this field.

The material in each of the subsections has, in some measure, been arranged chronologically so that the development of our understanding might be followed. Of necessity, the earlier points of view, some of which were subsequently repudiated or corrected by the original authors or by others, had to be included as presented in their first published state. Some of these earlier views, although not at present tenable, may serve as a framework for further research. Others of these earlier views now considered true may, in the same way, prove to be otherwise; for instance, Cooke's postulation[23] regarding the specificity of the house dust antigen.

The last most extensive critical review of the subject was made by Walzer[66] in 1938.

The present review discusses, in order, the following aspects of the problem; the question of the specific antigenicity of house dust; its chemistry; its biological, chemical and clinical relationships to moulds, bacteria and other inhalants; the preparation, purification and standardization of the extracts both chemically and biologically; the diagnostic considerations; the therapeutic utility; and the objective evaluation of the clinical results.

In 1921, Kern[43] wrote, "The sensitivities to other dusts, as for example to the dust of dirty cotton mattresses, woolen rugs, and mattings, are unique in that skin testing for the specific type of material is negative," thus calling attention to a new inhalant factor in respiratory tract allergy. Cooke[23], in 1922, demonstrated that house dust was a definite etiological factor in the production of bronchial asthma and at the same time assumed that individuals sensitive to dust did not necessarily show sensitivity to other substances used as testing materials. He felt that there was no agreement between dust extract sensitivity and sensitivity as demonstrated by other extracts. He concluded, therefore, that house dust contained an antigen peculiar to itself.

Spivack and Grove[58] reported in 1925 that in normal individuals the sites sensitized with the sera of house dust sensitive patients and subsequently exhausted with house dust extract nevertheless reacted positively to tests with other inhalants. The serum of a patient sensitive to both horse serum and to house dust was used for passive transfer site exhaustion experiments. Following exhaustion of the sites with horse serum, reactions to house dust were demonstrated as evidence of the specificity of the house dust antigen.

Van Leeuwen et al[62], in the same year, attempted to correlate the dust allergen with mould activity by noting that Aspergillus fumigatus, acting upon new kapok, produced a new extract capable of producing positive skin reactions. Frugoni and

Ancona[38] are credited with an original observation in reference to the appearance of the dust antigen in aging feathers.

Grove and Coca[39] at this time reported that the removal of nitrogen from extracts of pollen, house dust, horse dander, and green peas by digestion and dialysis caused no reduction in skin activity for pollen and dust extracts but a marked reduction in the extracts of horse dander and green peas. They concluded that the atopens present in pollen extracts and in dust extract were not, or did not seem to be, of the usual protein character common to other extracts.

In 1926, Rackemann and King[53] advanced two theories for the causation of bronchial asthma. They considered that the prime factor in the first group of supposedly house dust sensitive patients was not the dust sensitivity which ordinarily causes no symptoms, but the presence of the respiratory infection which affected the portal of entry and allowed dust to become absorbed more readily. There was a second group of patients in whom bacteria alone were responsible, the patient responding with a true hypersensitivity to a substance native to the bacteria or occurring as a product of their metabolism. They felt that the skin reactions to house dust were relatively unimportant since extracts of house dust prepared by Coca's method, and injected intradermally, failed to cause reactions of the urticarial type. As a corroborative evidence they cited the absence of constitutional reactions and the disappointment which resulted from attempts to hyposensitize patients with house dust extract. They were unable, however, to furnish proof of bacterial hypersensitivity by the production of immediate, local reactions of the urticarial type.

In 1927, Rowe[55] reported that 45 per cent of his patients, suffering from bronchial asthma, demonstrated a positive skin test to house dust extract. In seventy patients sensitive to house dust, by skin test reaction, there were numerous reactions to other inhalant proteins of animal origin. The author felt, therefore, that "reactions to house dust might be due to dust arising from certain articles of furniture rather than from some unknown source," as had been suggested by Cooke. Rowe concluded, therefore, that the possibility of an unknown specific substance in house dust was unlikely.

Ramsdell and Walzer[54] reported in the same year that, as demonstrated by the Dale technique, they had been unable to sensitize guinea pigs with a dialyzed dust extract, and therefore concluded that dust extracts had little or no antigenic properties for this test animal. In 1934, however, Harrison[41] using an alum precipitated extract was able to sensitize guinea pigs to house dust extract much more successfully.

In 1929, Cohen[15] published data demonstrating that nineteen of two hundred patients, who gave large skin tests to dust made from their mattresses, although they did not react to cotton or kapok, achieved complete relief when the offending article of furniture was eliminated. Recurrences could be prevented when mattresses were covered with impervious materials. At this time, Cohen considered moulds to be responsible for the change in the antigenic qualities of the mattress. In a later communication, in 1935, Cohen, Nelson, and Reinarz[21] eliminated moulds as a factor in house dust sensitivity. Five patients who gave positive skin tests to house dust only were tested with extracts of moulds obtained from the samples of dust to which they were sensitive, with none reacting. In the collection of house dust for the testing of such patients, samples from rugs and draperies which might contain many contaminants were avoided and the dust taken from bedding and overstuffed furniture was preferred. It was observed that an allergen developed in cotton linters as a result of aging, and that passive transfer experiments proved an identity of dust extract and linters extract, since either would neutralize the reagins for the other in a dust sensitive serum injected into a normal skin. It was also possible to demonstrate the fact that the protein responsible for cottonseed sensitivity differed

from that developed in aging cotton linters. Fresh cotton linters failed to give positive reactions in ten dust sensitive patients, but the same linters, aged in various ways, gave positive skin tests. The evidence suggested that house dust antigen was a degenerative product of cotton linters.

Walzer[66], discussing the experiments of Cohen and his colleagues, noted that they had not proven that the degenerative product of cotton linters (or of kapok or feathers) was a combination of degenerative products which made up house dust, or whether it was a single end-product of all such substances. He further criticized their work on the basis that dust reagins were not demonstrated in his ten subjects who, negative to fresh cotton linters, proved positive to extracts made from aged linters. He noted also that no report had been made of the degree of positive skin reactions with this extract in normal control subjects.

Cazort[12] then compared linter extracts made under varying conditions of light, heat, moisture and contamination with antigenic dust. He found positive skin tests to be present with these extracts in all of the patients sensitive to house dust extract and, again, was unable to prove the presence of any antigenic properties in extracts made from fresh cotton linters. In answer to Walzer's criticism of the work of Cohen and his colleagues, Cazort showed that the serums of dust sensitive patients used for passive transfer experiments reacted to extracts of old cotton linters, but not to the extract of new linters.

Wagner and Rackemann[63], having noted that Cooke in his original work on house dust had failed to consider kapok as a common allergen, made a number of studies concerned with this substance. They discovered that many of their asthmatic patients gave positive skin tests to extracts of old kapok fibre, and that the removal of the offending mattresses, pillows, and stuffed furniture afforded relief. Dusts taken from kapok produced large skin reactions in nine of ten asthmatic patients. Tests with the extract of the kapok fibre, the seed, and the hull proved the active ingredient to be contained in the fibre. It was presumably on the surface, freely soluble, and readily removable. Dialysis with cellophane removed the greater part of the active principle. The extract was not changed by boiling, but the active principle could be adsorbed on charcoal, and gave a positive Molisch and a negative Biuret test. Their work suggested that the activity of kapok was not a function either of the nitrogen factor or of the total solid content and that the nitrogen so obtained was not wholly protein in nature. In addition to other qualities, the extract could not be used successfully to sensitize guinea pigs.

Further studies with skin tests demonstrated that, of five normal subjects, two gave positive reactions. Walzer[66] suggested that these two positive reactions were due to the irritative properties of the extract and as a further indication that these reactions might be irritative, cited a group of thirty-eight supposedly kapok dust sensitive patients, in only ten of whom reagins were found to be present.

At this time, the mould theory of the origin of dust as advanced by van Leeuwen[62] was reconsidered by Feinberg[35] who reported that half of his dust sensitive patients reacted to fungi, while Brown[9] stated that skin tests to their own dust gave positive reactions in dust sensitive patients, although they often reacted negatively to dust derived from other sources. Although scratch tests made with extracts of moulds obtained from mattresses or house dust failed to give positive reactions, there were immediate urticarial reactions when tests were performed with the original mattress and dust extracts. The author nevertheless felt that moulds were important factors in the symptoms in dust sensitive patients, although he was unable to prove the presence of an allergenic substance produced by the action of moulds or bacteria upon dust. Lamson and Rogers[44] were also unable to substantiate the theory that mould sensitivity was a determining factor in the cause of house dust reactions.

Rackemann[22] returned to his earlier work with kapok, in order to determine what

part, if any, was played by moulds in the phenomenon of dust sensitivity. Since old and new kapok reacted so differently both chemically and clinically, it might be possible that the flora in old kapok was the cause of this difference. Patients sensitive to dust brought in samples of kapok, feathers, cotton, wool, and various types of animal danders and the samples were subjected to conditions favorable to mould growth. It was shown from the culture of fifty samples that no one mould grew on all of the substances of a certain type, nor was there a single mould, or a combination of moulds, specific to the environment of any one individual patient. Although kapok grew more moulds than any other material, it did not harbor any specific mould or combination of mould spores. The authors were unable to demonstrate positive skin test reactions to the moulds in all dust cases.

In 1937, Wagner and Rackemann[64] again attempted to establish the nature and the cause of the antigenicity seen in old kapok and not present in new kapok. Sterilization of extracts of kapok produced no deleterious effects upon the skin active principle. Cohen's experiment with cotton linters was repeated with kapok. The fresh fibres were sterilized and kept sealed for six months, after which period it was found that there was no active principle present as evidenced by the subsequent negative skin tests. It may be emphasized at this point that in Cohen's experiments the reactions to those samples which were left in open jars were larger than those in sealed containers. Walzer also noted that Cohen used fresh material and that it was not as new as the material studied by Rackemann and Wagner. These authors discovered that heat, moisture, oxygenation and carbon dioxide did not influence the antigenic activity of fresh kapok. Moulds obtained from a batch of old kapok as well as from old cotton linters and from house dust, and incapable of giving positive skin tests were sprayed into sterile jars containing sterile fresh kapok fibre, bale cotton, and absorbent cotton. The extracts made from these materials after they have stood for sixty days gave positive skin tests, but less so than did extracts made with old kapok. As the materials stood for longer periods of time the positive skin tests produced were larger. The repetition of the experiments with B. subtilis resulted in skin tests which were larger than those due to the extracts listed above. The authors concluded that the breakdowns in the kapok fibre were probably due to the effect of the growth of moulds upon the kapok and that the combination of moulds and kapok gave a positive skin test, although each of the original substances might give negative tests. Since this work was done with direct skin testing and the extracts obtained with B. subtilis gave larger reactions than did the mould extracts, Walzer noted that the mould theory of the cause of dust sensitivity could not be finally accepted until more evidence was presented.

In their subsequent studies, Wagner and Rackemann[65] noted that when a patient was sensitive to any one of the four substances, namely house dust, kapok, cotton linters and chicken feathers, he was frequently sensitive to the others. It appeared that a possible inter-relationship existed between the different dusts of household origin. The sera of patients sensitive to these substances were used for passive transfer exhaustion tests with the purpose of eliciting such cross reactions as might be present. No constant relationship between the four varieties of domestic dusts was discovered. Such variations as did occur depended on the reagin content of the different sera. *In vitro* tests were equally unsatisfactory in proving cross relationships between the four substances listed. It appeared that desensitization of passive transfer sites with kapok affected the dust and feather reagins but that exhaustion of the sites with either of these substances did not fully affect the kapok reagins. A comparison of the two methods of testing by direct skin tests and by mixtures of sera and antigens revealed discrepancies which, theoretically, should not have been present. The authors concluded that kapok, cotton linters, house dust, and feathers were not identical in their biological reaction in spite of the fact that many patients reacted to all four, and that studies of cross relationships using an *in vitro* method depended

on the reagin concentration of the sera for their final results. It appeared that none of the substances contained a common principle.

Since the studies were made upon eighty allergic and thirty non-allergic individuals, the first demonstrating positive skin tests in 64 to 81 per cent and the second group in 42 to 67 per cent, Walzer[66] contended this was further evidence of the irritative properties of the extracts used, since the distinction between atopic and normal groups of subjects was much less definite than is generally supposed.

Pratt[52] was able to demonstrate reagins in twenty of twenty-five patients, but the reactions were not considered as indicating a specific hypersensitivity, but rather as due to irritation. Walzer also drew attention to the phenomenon that positive passive transfer tests did not occur as frequently with 1+ reactions in cotton linter, dust, feathers, and kapok sensitivities as it did with other antigens.

Hill[42], however, considered all of the positive reactions in eczematous children as specific and not as being irritative in nature, since adequate control studies with normal infants of the same age group demonstrated no positive skin test reactions. It is generally known, however, that the infant's skin is less sensitive not only to dust but also to histamine, which again raises the question as to whether or not slight reactions to house dust and to similar dusts are specific.

Albert, Bowman and Walzer[1] studied fifty-four atopic individuals of whom twenty-two manifested a 1+ reaction to house dust. Of these, eighteen gave positive passive transfer reactions; twenty-four gave a 2+ reaction, of which two-thirds could be transferred, eight gave a 3+ reaction, all of which gave positive passive transfer results. In every instance in which dust reagins were present, reagins were also present to other dust producing inhalants, such as wool, feathers, or silk. In other series of ninety-seven children, seventy-two demonstrated reagins for house dust, and a positive passive transfer was present to one or more other inhalants whenever dust sensitivity existed. Reagins for pollen extracts and for foods, however, were found to occur independently of the reagins for house dust. In the following year, Walzer questioned the specific nature of dust in spite of the work listed above and concluded that the nature of the house dust antigen was unknown, since dust reactions were consistently related to positive skin test reactions to other inhalant substances. Pratt, however, was definitely able to state that in two patients of a group of fifty-six children reacting to house dust, there were reactions to house dust alone as corroborated by the presence of reagins.

Coulson and Stevens[24] brought a new and complicating factor into the picture by showing that there was a nonspecific substance in house dust which could be used to induce anaphylactoid symptoms in unsensitized guinea pigs. While studying anaphylactic sensitivity to a water extract of both house dust and of cotton linters as demonstrated in guinea pigs previously sensitized by subcutaneous injections of alum treated extracts, anaphylactoid symptoms were observed following an initial intravenous injection of water extract of house dust in unsensitized guinea pigs. This was interpreted by the authors as evidence of a nonspecific toxic factor present in the house dust extract.

Friedman[37] demonstrated in 1939, that guinea pigs sensitized with a 1 per cent alum precipitated house dust extract reacted anaphylactically in thirty to forty days to intravenous injections of house dust extract. Eighteen of twenty guinea pigs demonstrated positive Dale reactions and eleven of twelve demonstrated sensitivity by the intestinal or uterine strip technique. In eleven of twelve animals the *in vitro* test for sensitivity done on strips removed before the animal was shocked demonstrated contraction while only two of twelve animals dying in anaphylactic shock responded to house dust extract. All responded to histamine stimulation. In ten animals there was evidence of desensitization *in vivo*. Anaphylactic death could not be induced with the intravenous injection of house dust unless the dose was more than 0.1 c.c.,

but anaphylactoid reactions could be induced by intravenous injections of 1 c.c. The authors, with justice, conclude that the narrow working range between the minimal shocking dose and the dose which includes nonspecific anaphylactoid reactions is a serious handicap in the application of these techniques to the investigation of the nature of the house dust antigen.

Cohen and the co-workers[20] using cotton linters taken from the center of a bale of stored cotton, which therefore did not contain other epidermal substances or antigens, made a 1:50 dialyzed extract for investigative purposes. He reported that 90 per cent of his clinically dust sensitive patients gave a reaction which was 1+ or larger and that allergic individuals not sensitive to dust and normal controls gave negative skin tests. Eleven of twelve patients giving positive reactions gave 1+ or larger passive transfer reactions in the presence of completely negative controls. Using an alum precipitated extract of cotton linters, he was able to sensitize and shock guinea pigs who, reacting to cotton linters extract, could not be shocked by extracts made from cottonseed itself.

Hampton and Stull[10] prepared extracts made with dusts from individual sources and one from several sources. They concluded from the animal experiments that house dust extract contained an antigen other than that found in the known inhalants used for testing purposes and that this antigen was common to three different types of dust extract. In a series of 147 sensitized guinea pigs, cottonseed, cotton linters, kapok, raw silk, orris root, glue, pyrethrum, wool and other inhalants failed to produce positive Dale tests.

In an extension of their earlier work, Coulson and Stevens[25] thought that greater significance should be given to cotton linters as a possible source of the house dust antigen. They successfully sensitized eight guinea pigs to a water soluble antigen present in linters and failed to produce anaphylactic shock with a cottonseed extract made from the kernels of the cottonseed. The guinea pigs, however, demonstrated anaphylactic reactions to each of three different house dust extracts. Crossed reactions with extracts of house dust revealed differences in potency although there was an antigen common to all three extracts. Since the dialysates, however, were unable to produce anaphylaxis in guinea pigs sensitized to the respective extracts, the earlier work of Grove and Coca was confirmed. Crossed reactions with extracts of house dust and of cotton linters indicated that an antigen common to both might be present. Guinea pigs sensitized to house dust could be desensitized with dilute linters extract and were then incapable of being shocked with intravenous injections of concentrated linters extract. The fact that such guinea pigs could be then put into fatal anaphylactic shock with dust extract seemed to infer that beside the common antigen there might be another in house dust extracts. In several cases, fatal anaphylaxis occurred when animals sensitized to house dust extract reacted to shock doses of wool, implying that house dust extract might contain an antigen present also in wool. Since some guinea pigs sensitized to egg white were also fatally shocked by the dust extract which might, therefore, contain egg protein, the authors concluded that samples of house dust are variable and complex with respect to their antigenic content and that antigens allied to those in cotton linters, egg white, and wool were present. They were unable to demonstrate the presence of a single characteristic antigenic entity in house dust.

Davidson[26], studying a group of ninety-five dust sensitive patients, compared their reactions to house dust. By skin test techniques, horse dander was the most common, single, positive reaction, followed in succession by cow dander, cat dander, cottonseed, pyrethrum, and glue. The author therefore concluded that house dust possessed an antigenicity due to the substances it contained.

In 1942, Boatner and Efron[3] were able to prepare allergenically potent concentrates of dust by subjecting aqueous extracts to two successive fractional precipitations

with dioxane, followed by two successive precipitations from concentrated ammonium sulfate solution, dialyzing their final substance. The purified fraction appeared as a dark brown, glossy solid completely soluble in water and exhibiting some of the chemical properties of both carbohydrates and protein.

Sutherland[60] reviewing the literature relating to the chemistry of allergens with special reference to house dust, described the isolation of a polysaccharide containing fraction which, after the removal of all protein, demonstrated considerable activity.

Efron[28] later described his house dust substance as a fine, greyish powder formed by the aging of the materials from which household articles, furniture and clothing are composed and as physically, chemically, and biologically different from the original source materials. He did not deny that samples of house dust might contain many differing substances derived from furnishings, and affirmed that the ordinary house dust extract was diluted with adulterants and that this in turn was responsible for the necessity of intracutaneous testing, since the dust possessed a low, antigenic content. This was evidenced by the infrequency of constitutional reactions.

His most recently purified house dust extract is however sufficiently potent for scratch test purposes in the greater proportion of dust sensitive individuals and evidently possesses such high antigenic content that it produces frequent constitutional reactions. With this extract, patients who have previously shown no positive skin tests have been diagnosed as suffering from respiratory tract allergy due to dust alone. In patients with multiple sensitivities, the house dust test is large, if not larger, than that produced by any of the other allergens presumably present. He infers that it is not so much that dust possesses an antigenicity due to the presence of kapok, feathers, or cotton linters, but rather, that the patients who are negative by skin test to the materials listed when new but positive to the same materials when aged, are reacting to substances which contain properties common to house dust.

No review of the subject of house dust would be complete without a brief description of the many methods by which its extracts have been made. The house dust was not only obtained from varying sources, but quite obviously must have varied in potency and in irritating qualities. The methods of preparation were so diverse that this alone might help to explain some of the confusing differences discovered in the incidence of dust sensitivity and in the varying results of investigation. The extracts used were not standardized chemically or physically and only recently has any house dust extract been standardized biologically.

Kern[43] used a crude alcoholic extract of dust collected from patients' homes. The material was allowed to stand for several days in 14 per cent alcohol and then filtered before use.

Coca[13] defatted dust with carbon tetrachloride and with ether and extracted the material in his alkaline antiseptic solution. It was concentrated by evaporation, kept acid with carbon dioxide, dialyzed against Coca's fluid, and Seitz filtered, and then tested for sterility before use. Cooke[23] prepared his dust extracts in essentially the same manner. Rowe[55] used 0.5 per cent salt solution (as suggested by Piness[51]), as a substitute for Coca's extraction fluid.

Spain and Newell[57] concentrated the allergen in house dust extract by ultra-filtration through cellophane. The residue of colloidal material left on the filter membrane contained practically all of the activity of the original extract, free from color and a great deal of the extraneous matter.

The cotton linters extract prepared by Cohen was dialyzed in a cellophane bag in running water for forty-eight hours, and the extract then passed through filter paper and subjected to Seitz filtration before being dried in 30 c.c. quantities for storage in vacuum. When required, the residue was re-dissolved in 30 c.c. of sodium chloride

(0.85 per cent) containing Merthiolate (1:20,000) and a dilution (1:50) of this solution in 0.4 per cent phenol and 0.85 per cent sodium chloride was used for intracutaneous testing. Although the technique for lyophilization is now generally known, Cohen's original paper[17] should be consulted for the most exact details of adapting this process for the preservation of dust and pollen extracts for the small laboratory.

Hampton and Stull[40] prepared their dust extracts with carbon tetrachloride. After filtration and evaporation, the dust was extracted with a mixture of sodium chloride (0.5 per cent) and sodium bicarbonate (0.3 per cent) for twenty-four hours under toluene at 7°C. The extracts are separated from the solid material by a meat press and dialyzed against water under toluene for twenty-four hours. Following the addition of sodium chloride and sodium bicarbonate, the dilution is Seitz filtered and the extract so standardized that 0.00001 mg. protein nitrogen equals one unit.

Sutherland[59] prepared his house dust extract by wetting 500 gms. of dust with N/10 ammonia, and allowing it to stand for twenty-four hours before wrapping the mass in cloth and squeezing it through a press. The resulting muddy fluid is filtered through paper Seitz filters until a clear yellowish filtrate is obtained. Sodium benzoate (20 gms. liter) is added. Hydrochloric acid (1:15) is then gradually added until the mixture becomes slightly acid to Congo Red. A precipitate of benzoic acid appears in twelve to twenty-four hours and is filtered off in a Burhoes funnel and allowed to dry. The active principle is said to be adsorbed on the precipitate and released when the benzoic acid is dissolved in acetone. Any remaining precipitation is removed by centrifugalization. The material is washed repeatedly in acetone and finally in dry ether and allowed to dry. The resulting brownish amorphous powder is found to show great activity and is reported as providing an ideal testing agent.

In a series of papers by Efron, Boatner, and Dorfman[4,5], there is described a method of preparing house dust extracts free from large amounts of non-allergenic material. The extracts are highly purified and concentrated and are more active allergenically than any other extracts so far used. These extracts produce uniform strong positive reactions by the scratch method in clinically proven dust sensitive individuals. For the exact details of manufacture, the original papers, which are generally available, should be consulted. The dust extract is available commercially and will give positive skin tests in dilutions varying from 1:50,000 to 1:5,000,000.

Efron[28] has more recently described an improved method of the purification of house dust extracts based on the principles of his earlier papers, but with a slight modification. There are now available both therapeutic and diagnostic solutions, the former consisting of a glycerinated 2.5 per cent stock concentrate from which the appropriate dilutions may be prepared for treatment. The latter consists of glycerinated 0.5 per cent solution of the principal extract and as such is used for scratch testing or appropriate dilutions used for intracutaneous testing.

As regards the specificity of such extracts, Bowman and Walzer[6] pointed out that crude house dust extracts were irritating and that even large reactions should be read conservatively unless the presence of reagins could be demonstrated. Walzer noted that Bowman was unable to obtain completely negative skin reactions to ordinary crude stock house dust extracts by the intradermal method in a series of control patients and that further dilution of the extract to the point of dispossessing it of its irritating properties deprived it of its value as an effective diagnostic agent.

Feinberg[63] stated that there were no absolute criteria to determine whether or not a positive reaction to house dust represented a specific sensitivity. Efron[28] pointed out that the wide variations found in the incidence of house dust sensitivities were to be explained chiefly on technical differences, namely that, heretofore, house dust extracts had not been purified and standardized biologically. He stressed the fact that scratch tests as a rule did not elicit irritative reactions.

Cooke[23] using intradermal testing techniques found one-third of 327 cases of

hypersensitivity as due to house dust. It is interesting to note that this figure is much lower than that reported in more recent studies.

Meyer[46] considered house dust to be a primary factor in 57 per cent of 235 asthmatic patients as evidenced by skin tests with both stock and autogenous extracts.

Brown[7] was able to demonstrate positive skin test reactions to house dust in forty-seven of 100 patients presenting symptoms of bronchial asthma.

Rowe[55] obtained positive skin tests to house dust in 45 per cent of his patients with bronchial asthma. Two-thirds of the patients showing positive skin test reactions to dust gave histories suggestive of clinical sensitivity. A large proportion of these patients gave positive skin tests to other inhalant substances. Peshkin[49] (1926) summarizing the earlier work concerned with house dust, stated that he did not believe that house dust was the most important etiological agent in the bronchial asthma seen in his series of children studied. The same author[50] prepared house dust extract according to Coca's method and found the intradermal technique to be superior to that using the scratch type of application.

Pratt[52] tested seventy-one children who suffered from symptoms of perennial bronchial asthma by means of the intracutaneous method and was able to demonstrate sensitivity to house dust by passive transfer in 78 per cent of the subjects. Two of the subjects failed to react to one other substance and the author states that with multiple sensitivities present, the evaluation of house dust as a clinical cause of bronchial asthma is very difficult.

Cazort[12] using the intracutaneous method found that 74 per cent of 574 cases of perennial bronchial asthma gave positive tests to one or more of 140 allergens, and that about 45 per cent of this number reacted to house dust. Fourteen patients reacted to house dust alone.

Montgomery[47] demonstrated positive skin reactions to dust in forty-four of fifty-seven cases of bronchial asthma or 77 per cent. He described seven patients in whom the positive reactions were limited to dust alone.

Buffum and Freedman[11] reported 101 cases of bronchial asthma in children. Of these patients, seventy-eight had perennial bronchial asthma and twenty-three suffered from seasonal bronchial asthma. Using the scratch test method forty-five of the patients responded with positive reactions ranging from 1+ to 4+. With the crude type of dust extraction, nineteen of seventy-five reacted to autogenous dust extracts. The relationship between the dust reactions and those to other inhalants was shown by 75 per cent of thirty-four patients, who, reacting to animal inhalants, also reacted positively to dust. The nine patients who were dust negative gave weak reactions to animal inhalants, while house dust sensitive patients gave strong reactions to both house dust as well as to animal inhalants. Skin test reactions to foods occurred independently of the dust reaction. Of forty-two patients reacting to pollens, twenty-five were dust positive and seventeen dust negative. In eight patients in this series, dust alone was considered as the exciting cause of the bronchial asthma as demonstrated by the fact that improvement was immediate when the offending agent was diminished or removed. Of 101 patients, thirteen were severely asthmatic and of these, eleven gave positive house dust reactions and four were proven clinically sensitive to household dust.

An analysis of the reported incidence of specific house dust sensitization from the work of a number of investigators shows that the figure varies from 45 to 79 per cent in patients suffering from bronchial asthma.

Of interest in this regard, is the suggestion by Cazort[12] who states that patients with bronchial asthma, sensitive to house dust, generally seek diagnostic studies during the Fall and Winter and have their longest remissions during July and August. The patients usually give a history of prolonged nasal irritation worse at night and during the early hours of the morning. He is usually worse at home.

Efron[28] however felt that it was not necessary to correlate the history and the specific sensitization. It was not always possible to distinguish between the irritant and the allergic reactions following exposure to house dust and almost all patients with respiratory tract allergy are aggravated by such exposure.

In explanation of these varying previous studies, Dorfman and Efron[27] devoted their attention to the effect of varied dilutions of house dust extract upon the skin when the scratch method of testing is used. They found that the skin test curve obtained with serial dilutions of house dust was a discontinuous one, so that in a given subject, a given size skin reaction could be produced by potencies of extract which varied greatly. Equally sized skin reactions might denote a very wide range of potency of the extract, and a tendency toward similar sized reactions was present in the upper ranges of the concentrations used. A plateau might, however, occur at any level of concentration and with reactions of any size. The discontinuity of the skin reaction curve was obtained despite the presence of factors which affected the size of the skin reactions and which might tend to produce unequal reactions even of extracts of the same concentrations and amounts. The authors later applied the use of the comparative skin reaction curve to the determination of the skin reacting potency of house dust extracts and, using a scratch test technique, demonstrated differences in the reactivity of the skin between the radial and ulnar sides of the forearm. Dilutions of the same dust were then made and comparative skin test curves studied. Using two separate dust extracts for the dilution method and the parallel scratch test technique, it was possible to make a biological assay of the potency of the extracts.

In an extension of their studies, Pabst, Boatner, and Efron made comparative tests on forty house dust sensitive patients, using several dilutions of the identical extract and found no significant difference in the size of the reaction between the radial and ulnar sides of the forearm. Using two extracts, one of which was twice as concentrated as the other, 403 comparative skin tests were performed on fifty-five house dust sensitive patients. These tests performed by the scratch technique reveal a significant difference between the two extracts. The authors concluded that these significant differences in the sizes of the reactions when different extracts were tested were attributable to the differences in extract potencies and not to be sampling errors in the testing technique. In this paper, the authors established the use and importance of the chi-square test method for the statistical analysis of comparative skin tests. In their next successive paper, the same authors presented an extract method of estimating the probability associated with a given value of chi-square for an analysis of comparative skin test reactions.

The continuation of the work by the same authors consisted of a study made by means of the scratch test using purified house dust extract upon two groups of patients. The first, a controlled group of 200 subjects, gave negative present and past histories of any allergic symptoms. The second group consisted of 160 patients presenting symptoms of perennial hay fever or asthma or both, although in this group the symptoms were not always produced by exposure to house dust. The purpose of the tests was to establish a diagnostic efficiency of the purified dust extract referred to above. As a base line for their studies they defined their concepts which can best be given in their own words as "the presumptive evidence of sensitization to a ubiquitous substance by skin tests depends upon the demonstration of a typical skin reaction to an extract of such a substance, which extract, when applied in identical concentration and quantity in previous tests, is shown to produce a significantly greater incidence of typical skin reactions in a series of patients, whose symptoms could be attributed to that substance than in a series of individuals having no disease attributable to this substance." An irritant extract was defined as "one which produces positive skin reactions in a percentage of control cases, not significantly different from the percentage produced in patients whose symptoms are attributable

to the particular substance in question." The diagnostic efficiency of an extract depends upon the relationship of the percentage of positive reactions in these two groups.

In the control series the skin reactions with varying dilutions was found to be 7.5 per cent and in the allergic group 78.1 per cent. Dividing the sum of the two by the incidence of the allergic group results in a fraction 0.912 and suggests that a positive skin test with this extract is diagnostic of allergic disease attributable to house dust in 91.2 per cent of the instances in which the test is positive.

Further studies by the same authors[33] evaluated the significance of postive reactions to intracutaneous tests performed with the purified house dust extract. Two groups of patients were studied, the first, a control group of sixty-seven subjects with no history of allergy who showed no reactions to scratch tests with house dust and a second group consisting of seventy-five patients presenting perennial symptoms of hay fever or bronchial asthma or both, all of whom gave positive scratch tests to house dust extract. The tests were done intracutaneously with 0.01 c.c. quantities of concentrations ranging from 0.002 to 0.000002 per cent of the original house dust extract. The dilutions represented serial dilutions of a 0.1 per cent solution of house dust in 50 per cent glycerin containing 0.4 per cent phenol. The authors found that extracts of the house dust up to and including 0.002 per cent solutions were not irritating and the reactions produced up to the concentration of 0.002 per cent were allergenic in nature.

In the final paper of the series, Efron[29] presented a carefully worked-out thesis for the adoption of the biological method of standardization for house dust extracts. Since the extracts cannot be made constant in potency, are subject to deterioration, and the reactions are not at all times exactly reproducible, and since the chemical and physical measuring techniques such as the total nitrogen, the protein nitrogen, the weight by volume, or the Noon unit are, at best, not too reliable, it is best to base our criteria of the allergenic potency upon (1) the specificity of skin reactions (2) the diagnostic probability of specific skin reactions and (3) the comparative size of specific skin reactions. In considering the specificity of skin tests, one must be careful to distinguish between specific and nonspecific reactions. The latter can be due to irritation, primary urticariogenic substance content or to nonspecific properties, such as concentration or glycerin or histamine content. The difference in incidence of positive reactions in a series of allergic subjects and a group of non-allergic individuals may then be attributed to the substance itself. If the difference in the number and type of positive reactions is significant statistically, the skin reactions in both groups are considered to be specific. As an example, the following data is presented.

A solution of purified house dust (0.75 per cent) tested by the scratch test method gave fifteen positive reactions in 200 normal controls and 125 positive reactions in 160 allergic patients. Used in the same way, an ordinary house dust extract gave twenty positive reactions in thirty controls and sixty-five positive reactions in eighty allergic individuals. From the point of view of specificity of reaction, the latter series is obviously not statistically significant. Of course, another biological method of assaying solutions is an analysis of the difference in incidence of positive tests in passively sensitized sites and in the non-sensitized skin areas of control patients. In an elaboration of this point, Efron recalls that Black[2] first suggested that the reagin-allergen reaction is not the cause of the clinical symptoms and that it may be that some other substance is concerned in precipitating such symptoms. The following generally known phenomena attest to the fact that such a mechanism exists. It is a common experience that the incidence of specific sensitivity is significantly greater than that of clinical sensitivity. Specific skin reactions may antedate clinical sensitivity just as specific skin sensitivity may remain long after clinical sensitivity has disappeared. The symptoms of allergic individuals are

commonly intermittent. Specific reactions, therefore, may or may not be relevant to the presenting symptoms. Those that are relevant are the diagnostic reactions which constitute the clinically significant fraction of the total number of specific reactions.

The problem is by no means susceptible of simple solution. The observation that when comparing two extracts the skin tests may be larger, smaller, or of equal size, is not always an indication of the difference in the two extracts. The papers quoted actually state that "the curve of skin reaction sizes from different serial dilutions of an extract tend to plateau." For a given substance, a skin reaction of a given size can be produced by varying concentrations of the same extract, just as equally sized reactions may occur from extracts which vary widely in potency. Only differences of certain magnitudes are demonstrable by means of comparative skin tests. The authors show that when one extract has twice or more the potency of another, comparative skin tests reveal a difference. Whether or not smaller degrees of potency difference between two extracts are demonstrable by comparative scratch tests has not as yet been determined.

The studies mentioned would have little or no significance unless they could be correlated with the results of treatment, either passive, as by the elimination of the offending antigen or active, as by injection therapy.

Kern[43] presented a case of a thirty-six-year-old woman with symptoms of asthma present for fourteen years, perennially, and most marked during August and September. Skin tests were present to an extract made from her cotton mattress and to pollen extracts. On advising the patient to wrap the mattress with heavy paper there was prompt relief of symptoms. Whenever it was suspected that the offending agent was in the room of the patient with asthma, Kern suggested the removal of the furniture from the room with replacement of individual items over a period of time, in which manner the offending agent could easily be discovered and discarded.

In another of the early classic cases, Cooke[23] presented a twenty-eight-year-old male patient with asthma of fourteen years' duration whose skin tests were negative to extracts of the common emenations but whose symptoms were completely environmental in that they always occurred upon his return home. Extracts of dust from the patient's household gave positive intradermal tests. The author states that the failure of treatment of patients with multiple sensitization may be explained by the discovery of an exact single etiological agent.

Leopold and Leopold[45] were able to produce asthmatic attacks at will in a dust sensitive individual under controlled conditions of humidity, temperature, and barometric pressure. They found that the effects of these latter three factors were negligible.

Feinberg[34] presented four patients with bronchial asthma sensitive to house dust, all of whom responded favorably to hyposensitization.

Cohen[18] described the use of the mechanical air filter placed in the patient's home to make room pollen free as well as dust free. The filter proved to be satisfactory in removing 99 per cent of the pollen particles.

Brown[8] reported that in patients with bronchial asthma who were sensitive to cottonseed and to kapok the removal of the offending articles and their associated dust content brought on prompt relief.

Rowe[55] noted the value of testing with house dust extract as an indication of the type of sensitization causing the patient's condition. He felt that reactions due to house dust extract should make the physician suspicious of sensitization to other inhalants.

Cohen and Rudolph[19] reviewing 100 patients presenting ragweed hay fever reported that 30 per cent had slight symptoms at other times of the year. Of these patients, 70 per cent had seasonal symptoms only, and 36 per cent were sensitive to

substances other than ragweed pollen. It was concluded, therefore, that in the treatment of patients with ragweed hay fever other sources of sensitivity had to be eliminated or treated. In another paper, the same authors outlined a program for the treatment of dust sensitive asthmatic patients calling for the elimination of many sources of dust as possible. The elimination of the dust by daily cleaning was to be accompanied simultaneously with hyposensitization therapy.

Cazort[12] also recommended avoidance of dust during desensitization, the best results being obtained in the patients who gave the most strongly positive skin reactions. The poorest results were achieved in those patients who had chronic vasomotor coryza and slight skin reactions.

Todd[61] found the use of an autogenous dust extract more satisfactory than stock dust and claimed good to excellent results in over 70 per cent of his patients.

Buffum[10] reviewing sixty-four cases of bronchial asthma given general treatment and dust elimination, but no hyposensitization reported that 18.8 per cent presented no symptoms for one year, 43.8 per cent were much improved, if not almost entirely relieved, 31.2 per cent were improved, while 6.2 per cent were unimproved.

Montgomery[47] reported on the studies of fifty-seven cases of bronchial asthma over a two-year period of whom forty-four were skin sensitive to house dust extract. Of this number, thirty were chosen for study, since they had been under treatment for more than one year. Of these, eleven showed associated food sensitivities, six pollen sensitivities, and ten chronic infection. The patients were treated by elimination, pollen therapy, vaccine therapy and hyposensitization to house dust extract. Sixteen were completely relieved, seven markedly benefited, three achieved fair results, and four reported as complete failures. Montgomery concluded that house dust sensitivity was a common cause of bronchial asthma and in spite of frequent complications with other forms of allergy, good results could be obtained by suitable treatment.

Sutherland[59] desensitized twenty asthmatic soldiers with a 1 per cent solution of his house dust extract, the initial dose being 0.05 c.c. with increases at weekly intervals so that improvement of symptoms could be noted after twelve injections.

Efron and his colleagues[31] reported on the studies of seventy-two patients who suffered from bronchial asthma and hay fever from early September to the end of the following June, reporting freedom from symptoms during the summer months. All of the patients gave positive skin tests to purified house dust extract, and were treated with hyposensitization therapy over a period of nine to eighteen months. Treatment was initiated with 0.1 c.c. of a 0.0005 concentration of purified house dust, the increases being given according to the patient's tolerance with intervals from every two days to once weekly. Those patients who showed a moderate to marked improvement were little affected by weather. Local reactions were frequent and twelve of the patients experienced a total of eighteen constitutional reactions, the majority occurring in three. Dust elimination instructions were intentionally omitted as part of the program. In this group, thirty-seven (over 50 per cent) showed marked improvement; twenty-four (33 per cent) reported moderate improvement, six slight improvement, and five no change. The authors concluded that these results further established house dust as an important etiological factor in the causation of this type of bronchial asthma. Since the dust extract used in this work is commercially available, confirmation of these results is to be expected.

It is apparent from this review of the subject that dust sensitivity is common and that solutions made by many differing methods are effective in detecting such sensitivity and in treating it. When present, dust sensitivity is usually corroborated by the common criteria which may be listed as positive skin and passive transfer tests, improvement following elimination or injection therapy, which may be accompanied by constitutional reactions.

This review was written as a first part of the study of the background of the subject since no work had been done with the object of detecting the presence or absence of skin blocking antibodies as additional evidence of a somatic response to injection therapy. With the standardized solution as potent as that prepared by Efron, it was obvious that this would necessarily be one of the next studies to be done in this field. This work, dealing with immunological factors, and now in progress, will be published in the near future.

REFERENCES

1. Albert, M., Bowman, K., and Walzer, M.: Relation of the dust reaction to other inhalant reactions. J. Allergy, 9:392, 1938.
2. Black, J. H.: South. M. J., 21:373, 1925.
3. Boatner, C. H., and Efron, B. G.: Preparation and properties of concentrates of house dust allergen. J. Invest. Dermat., 5:7, 1942.
4. Boatner, A. H., Efron, B. C., and Dorfman, T. J.: Preparation of purified house dust extracts. Science, 91:389, 1940.
5. Boatner, C. H., Efron, B. C., and Dorfman, R. I.: Studies with antigens: preparations of purified house dust extracts. J. Allergy, 12:176, 1941.
6. Bowman, R., Walzer, M.: Coca, Walzer and Thommen: Asthma and Hay Fever in Theory and Practice. Springfield, Ill., C. C. Thomas, 1931.
7. Brown, A.: Present day treatment of asthma. J.A.M.A., 85:1151, 1926.
8. Brown, G. T.: Cottonseed and kapok sensitization. J.A.M.A., 93:379, 1929.
9. Brown, G. T.: Hypersensitiveness to fungi in relation to house dust. J. Allergy, 7:455, 1936.
10. Buffum, W. P.: Role of house dust in bronchial asthma. Rhode Island M. J., 20:73, 1937.
11. Buffum, W. P., and Freedman, S. J.: Relation of household dust to asthma in childhood. Rhode Island M. J., 22:42, 1939.
12. Cazort, A. G.: House dust antigen in allergy. South. M. J., 29:1022, 1936.
13. Coca, A.: Preparations of fluid extracts. J. Immunol., 2:1402, 1922.
14. Coca, Walzer and Thommen: Asthma and Hay Fever in Theory and Practice. Springfield, Ill.: C. C. Thomas, 1931.
15. Cohen, M. B.: Asthma due to household articles; report of nineteen cases due to dust from mattresses. J. Lab. & Clin. Med., 14:837, 1929.
16. Cohen, M. B.: Further observations on the use of filtered air in the progress and treatment of allergic conditions. J. Lab. & Clin. Med., 13:963, 1938.
17. Cohen, M. B.: New methods of preserving pollen and dust extracts. J. Allergy, 10:385, 1939.
18. Cohen, M. B.: Prophylaxis and treatment of hay fever and asthma in rooms made pollen and dust free by means of mechanical filters. J. Lab. & Clin. Med., 13:59, 1927.
19. Cohen, M. B., and Rudolph, J. A.: Hay fever: the importance of substances other than pollens in the etiology: their influence on seasonal cure. Arch. Int. Med., 45:742, 1930.
20. Cohen, M. B., Cohen, S., and Hawyer, K: Further observations on the house dust antigen. J. Allergy, 10:561, 1939.
21. Cohen, M. B., Nelson, T., and Reinarz, B. H.: Observations on the nature of the house dust allergen. J. Allergy, 6:517, 1935.
22. Conant, N. F., Wagner, H. C and Rackemann, F. M.: Fungi in pillows, mattresses and furniture. J. Allergy, 7:234, 1936.
23. Cooke, R. A.: Studies in specific hypersensitivity; IV. New etiological factors in bronchial asthma. J. Immunol., 7:147, 1922.
24. Coulson, E. J., and Stevens, H.: Sensitization of guinea pigs to cotton linters and house dust extracts. Proc. Soc. Exper. Biol. & Med., 40:457, 1939.
25. Coulson, E. J., and Stevens, H.: Antigenic relationships of cotton linters and dust and dust precursors. J. Allergy, 11:537, 1940.
26. Davidson, M. T.: Source of allergenic activity of house dust. J. Allergy, 14: 244, 1943.
27. Dorfman, R. I., and Efron, B. D.: Studies with antigens. J. Allergy, 9:464, 1938.
28. Efron, B. G.: The house dust factor in bronchial asthma. In Derbes and Englehart: The Treatment of Bronchial Asthma. Philadelphia: J. P. Lippincott Co., 1946.

29. Efron, B. G.: Standardization of extracts—Bioassay. In Derbes and Englehart: The Treatment of Bronchial Asthma. Philadelphia: J. P. Lippincott Co., 1946.
30. Efron, B. G., and Dorfman, R. I.: Studies with antigens: The use of comparative skin reaction curves in the determination of the skin reacting potency of house dust extracts. J. Allergy, 10:443, 1939.
31. Efron, B. C., Boatner, C. H., and Everett, P.: Treatment with purified extracts of house dust. New Orleans M. & S. J., 93:514, 1941.
32. Efron, B. C., Boatner, C. H., and Pabst, R.: Studies with antigens: significance of scratch test reactions to house dust extracts. J. Invest. Dermat., 3:401, 1940.
33. Efron, B. C., Boatner, C. H., and Pabst, M. R.: Significance of reactions to intracutaneous tests performed with extracts of purified house dust. J. Invest. Dermat., 4:95, 1941.
34. Feinberg, S. M.: Asthma due to house dust. M. Clin. North America, (July) 1927.
35. Feinberg, S. M.: Mold allergy: Its importance in asthma and hay fever. Wisconsin M. J., 34:254, 1935.
36. Feinberg, S. M.: Allergy in Practice. Chicago: Year Book Publishing Co., 1944.
37. Friedman, H. G.: Studies in guinea pig anaphylaxis with house dust antigens. J. Allergy, 10:479, 1939.
38. Frugoni, C., and Ancona, G.: Bronchial asthma. Policlinico (Sez. Med.), 32:161, 1925.
39. Grove, E. F., and Coca, A. F.: On the nature of the atopens of pollens, house dust antigen. J. Allergy, 10:561, 1939.
40. Hampton, S. F., and Stull, A.: Antigenic studies by Dale test: antigenicity of house dust. J. Allergy, 11:109, 1940.
41. Harrison, W. T.: Effect of alum-precipitated pollen extract on guinea pigs. Public Health Reports, 49:462, 1934.
42. Hill, L. W.: Sensitivity to house dust and goose feathers in infantile eczema: role of specific allergens. J. Allergy, 9:37, 1937.
43. Kern, R. A.: Dust sensitization in bronchial asthma. M. Clin. North America, 5:751, 1921.
44. Lamson, R. W., and Rogers, E. C.: The skin hypersensitivity to molds; an attempt to correlate this with clinical allergy. J. Allergy, 7:582, 1936.
45. Leopold, S. S., and Leopold, C. S.: Bronchial asthma and allied allergic disorders: preliminary report of a study under controlled conditions of environment, temperature and humidity. J.A.M.A., 84:751, 1925.
46. Meyer, G. P.: House dust in asthma. Atlantic M. J., 27:59, 1923.
47. Montgomery, L. G.: Asthma due to house dust. J. Indiana M.A., 30:18, 1937.
48. Pabst, M. R., Boatner, C. H., and Efron, B. G.: Studies with antigens, X the statistical methods for the analysis of comparative skin reactions. N. O. Med. and Surg. J., 93:579, 1941.
49. Peshkin, M.: Asthma in children. Am. J. Dis. Child., 31:763, 1926.
50. Peshkin, M. M.: Asthma in children. Comparative methods of skin testing with differently prepared extracts of house dust. J. Lab. & Clin. Med., 13:57, 1927.
51. Piness, G., Miller, H., and Alles, G. A.: Comparative methods of protein extractions. J.A.M.A., 83:608, 1924.
52. Pratt, H. N.: House dust hypersensitivity in perennial asthma of childhood. J. Allergy, 8:60, 1936.
53. Rackemann, F. M., and King, D. S.: Bronchial asthma: Role played by house dust and by bacteria. Boston M. & S. J., 195:347, 1926.
54. Ramsdell, S. G., and Walzer, M.: On antigens; antigenic properties of glue, wheat, and house dust. J. Immunol., 14:207, 1927.
55. Rowe, A. H.: House dust in the etiology of bronchial asthma and hay fever. Arch. Int. Med., 39:498, 1927.
56. Rudolph, J. A., and Cohen, M. B.: Management of the dust asthmatic. J. Allergy, 3:574, 1932.
57. Spain, W. C., and Newell, J. M.: Ultrafiltration of house dust extracts. J. Allergy, 7:134, 1936.
58. Spivack, C. A., and Grove, E. F.: Studies in hypersensitiveness: Study of house dust atopen in asthma. J. Immunol., 10:465, 1925.
59. Sutherland, C.: Preparation of house dust extracts. Brit. M. J., 2:280, 1942.
60. Sutherland, Charles: The allergen of house dust. M. J. Australia, 32:584, 1945.
61. Todd, R.: Dust allergy. South. Med. & Surg., (August) 1934.

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✶ *In Memoriam* ✶

WILLIAM WADDELL DUKE, M.D., F.A.C.A. (Hon.)

On April 10, 1946, William Waddell Duke passed away in Kansas City, Missouri, after a prolonged illness resulting from heart disease. Doctor Duke was born in Lexington, Missouri, on October 18, 1882. He was a descendant of a long line of physicians and a direct descendant of Dr. Ephraim McDowell. He received his Bachelor of Philosophy Degree at Yale University in 1904, and his Medical Degree from Johns Hopkins University in 1908. As a student at Johns Hopkins University, he worked in the Department of Physiology and wrote many papers in collaboration with Dr. W. H. Howell on the relationship between potassium and calcium salts and vagus inhibition of the heart beat. Together with Doctor Howell, he was the co-discoverer of the physiology of blood platelets and described methods for determining the bleeding time, coagulation time, and made pioneer observation on the relationship of blood platelets to hemorrhagic disease. He first described the Palm color test which is now known as the Duke test for anemia. He served his internship at the Massachusetts General Hospital in 1909. From 1910 until 1913 he studied at the Universities of Vienna, Berlin and Tübingen. There he was a student of von Pirquet, Schick, Eppinger and many others who were then performing the original experiments in anaphylaxis.

WILLIAM WADDELL DUKE

He was Professor of Experimental Medicine at the University of Kansas Medical School from 1914 to 1918, and Professor of Medicine at the Kansas City Western Dental College from 1921 to 1924. He first became interested in the subject of allergy in 1914 and was one of the early physicians to treat sensitive patients with injections of the offending protein. He was one of the first to describe food allergy as a cause of abdominal and genito-urinary pain. He was the first to suggest a relationship between allergic disease and the unusual response to physical agents such as heat and cold and gave the name of "physical allergy" to this phenomenon. His classical descriptions of sensitivity to light, cold, heat, mechanical irritation, physical and mental exertion made over twenty-two years ago are the basis today of all diagnostic and therapeutic measures in physical allergy. He wrote the first complete clinical textbook on allergy which was titled, "Allergy Asthma, Hayfever, Urticaria and Allied Manifestations." Published in 1925, it still today can be used as an authentic text.

He first described a method of testing for aspirin sensitiveness and a method for avoiding aspirin catastrophies. In 1930 he described the classical picture of facial de-

formity caused by nasal allergy which is known as the allergic facies. He first described soy bean as an important source of allergy. He was the first to do pollen counts in the Middle West and was the inventor of a machine and method for rapid and accurate determination of the pollen count in the air. In 1923 he persuaded Oren C. Durham, now a nationally known authority on pollen, to give up his work as a photographer and devote all of his time to the collection and study of pollens and set up a botanical garden where Durham's original pollen studies were made. He gave the first Allergy Exhibit at the Scientific Exhibit of the American Medical Association and was awarded the Silver Medal for Research in Allergy in 1924. He was president of the Association for the Study of Allergy in 1925 . He received the Forum of Allergy Award for Distinguished and Original Contributions to the Field of Allergy in 1942.

He was a fellow of the American College of Physicians, an Honorary Fellow of the American College of Allergists, fellow of the American Academy of Allergy and a member of many other medical societies. He was the author of "Oral Sepsis in Relation to Systemic Disease" in 1918. He wrote the chapters on Allergy for the Cyclopedia of Medicine, The Practitioner's Library of Medicine and Surgery and The Modern Home Medical Adviser. He wrote the Annual Review of Literature in Allergy as related to Otolaryngology for the *Journal of Otolaryngology* from 1926 to 1938. He prescented the Allergy and Physical Allergy Exhibit in the Hall of Science at the Century of Progress in Chicago in 1933 and 1934.

He is survived by his wife, Mrs. Frances Duke, and by two children, Henry Basil Duke and Suzanne Duke Scott.

Doctor Duke was gifted with a foresight in medicine that occurs but rarely. Much of his monumental work was so far ahead of his time that it was greeted with doubt and often derision. He had the courage of his convictions and lived to see his observations acclaimed and made part of the great contributions to medicine. He was original in his thinking and possessed of tremendous physical and mental energy. It will be many years before another of his talents appears.

C. M. K.

PROGRESS IN ALLERGY

(Continued from Page 240)

62. van Leeuwen, W. S., Bien, Z., Kremer, W., and Varekamp, H.: On the significance of aspergillus in the etiology of bronchial asthma. Ztschr. f. Immunitätsforsch, u. exper. Therap., 44:1, 1925.
63. Wagner, H. C., and Rackemann, F. M.: Kapok: its importance in clinical allergy. J. Allergy, 7:224, 1936.
64. Wagner, H. C., and Rackemann, F. M.: Kapok and moulds: important combination. Ann. Int. Med., 11:505,1937.
65. Wagner, H. C., and Rackemann, F. M.: Crossed reactions to household dusts. J. Allergy, 8:537, 1937.
66. Walzer, M.: Critical review of recent literature on the dust atopen and on vitamin C in relation to hypersensitiveness. J. Allergy, 10:72, 1938.

News Items

MARCELLE HYPO-ALLERGENIC COSMETICS, INC., ADDITIONAL GRANT

The College gratefully acknowledges receiving the sum of $500 for a Merit Scholarship Fund. This fund is to defray the attendance fee at any of the College Instructional Courses of residents or interns who are recommended by the committee for that purpose.

* * *

Ralph I. Alford, M.D., announces his return to the civilian practice of Allergy at his former location, 83 Park Street, Montclair, New Jersey.

* * *

Dr. Marion T. Davidson announces his return from military service to the practice of allergy, 819 Frank Nelson Building, Birmingham, Alabama.

* * *

Myron A. Weitz, M.D., and Louis E. Lieder, M.D., announce their return from military service and association in the practice of allergy at 327 Osborn Building, 1021 Prospect Avenue, Cleveland 15, Ohio.

* * *

Carl D. Marsh, M.D., F.A.C.A., announces the opening of his office for the practice of allergy and dermatology at 616 Goodwyn Institute Building, Third and Madison, Memphis, Tennessee.

* * *

Dr. Joseph L. Vinocur announces his return from military service and the resumption of the practice of allergy. He will be associated in practice with Dr. Benjamin Nozik, who expects to be released from the service in the very near future.

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Stanley F. Hampton, M.D., announces his return from military service and the reopening of former office for the practice of allergy and internal medicine, at 1018 Beaumont Medical Building, 3720 Washington Boulevard, St. Louis, Missouri.

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Acta Paediatrica, published in Stockholm, is now in our exchange library. This contains excellent articles on allergy in children. The articles are in English, and are available to the College members for review.

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We welcome the new *Journal of Geriatrics,* devoted to research and clinical study of the diseases and processes of the aged and aging. Volume 1, Number 1, January-February, 1946, has been received by the College library. There is an excellent article in it on "Bronchial Asthma with Special Reference to Its Elderly Victims," by Jonathan Forman, M.D., F.A.C.A.

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The attention of the readers of the ANNALS is called to the *Bulletin of Allergy,* which is devoted exclusively to the subject of allergy, and is published bi-monthly by Wyeth, Inc., and distributed to the members of the medical profession. Volume 1, Number 1, appeared in February, 1945. The cover of each issue has a portrait of the pioneers in allergy, together with a biographical sketch; there is one leading article in each issue on the various allergic diseases with a bibliography, followed by allergy abstracts.

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Dr. Harold Abramson of New York City, who served as a Lieutenant Colonel, Chemical Warfare Service, United States Army, has been awarded the Legion of Merit for his work in the Chemical Warfare Service. He was Chief of the

Physical Chemical Section, Chemical Research Branch, and Assistant Chief, Defense Materiel Branch at Edgewood Arsenal, Maryland, from July, 1942, to December, 1943.

Dr. Abramson is responsible for the successful development of penicillin aerosol.

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Drs. W. Randolph Graham and J. Warrick Thomas have announced establishing the Graham-Thomas Clinic, 201 West Franklin, Richmond, Virginia, which was formerly the Vaughan Memorial Clinic. Their practice is limited to allergy and internal medicine, and the new organization will offer recognized postgraduate training in allergy for qualified physicians and will also continue the training school for allergy techicians as they formerly did. They will continue to have the same location and are making arrangements to enlarge the clinic by taking over more space.

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We are pleased to announce the return from service of the following members of the College and their present locations: Major Glen I. Allen, 101 Cole Court, Peoria, Illinois; Captain Maurice C. Barnes (MC), 1310 Austin Avenue, Waco, Texas; Lt. Comdr. Norman W. Clein (MC), Children's Clinic, 1155 10th Avenue North, Seattle, Washington; Captain Julius J. Greenberg (MC), 3328 Fullerton, Detroit 6, Michigan; Captain George F. Hieber (MC), 5204 Tenth Street, St. Petersburg, Florida; Captain William Jacobs (MC), 1030 Stuyvesant Avenue, Irvington 11, New Jersey; Captain Meyer R. Lichtenstein, 1733 20th Avenue, Oakland 6, California; Captain David Mansowit (MC), Uptown Bank Building, 4753 Broadway, Chicago, Illinois; Major Carl D. Marsh, 616 Goodwyn Institute Building, Memphis 3, Tennessee; Major Raymond R. Preefer (MC), 470 Westminster Road, Brooklyn, New York; Major Nathan Schaffer (MC), 172 Arlington Avenue, East Orange, New Jersey; Captain Joseph L. Vinocur (MC), 10535 Carnegie Avenue, Cleveland, Ohio.

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A Pediatric Postgraduate Conference was held at the University of Texas School of Medicine, Galveston, Texas, on April 15 to 20, 1946; the course was sponsored by the University of Texas School of Medicine Committee on Postgraduate Education, Dr. George M. Decherd, Jr., Director. Distinguished guest speakers included the following: Dr. John A. Anderson, Professor and Head, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah; Dr. Ralph Bowen, Associate Professor of Pediatrics, Baylor University School of Medicine, Houston, Texas; Dr. Daniel C. Darrow, Associate Professor of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; Dr. J. H. Park, Jr., Professor and Head, Department of Pediatrics, Baylor University School of Medicine, Houston, Texas; Dr. Ralph Platou, Professor and Head, Department of Pediatrics, Tulane University School of Medicine, New Orleans, Louisiana; Dr. George Salmon, Associate Professor of Pediatrics, Baylor University School of Medicine, Houston, Texas; Dr. A. V. Stoesser, Associate Professor of Pediatrics, University of Minnesota School of Medicine, Chief of Pediatric Service, Minneapolis General Hospital, Minneapolis, Minnesota; Dr. James Watt, Surgeon, U. S. Public Health Service, Quarantine Station, Algiers, Louisiana. In addition to the guest speakers, twenty-nine faculty members of the University of Texas School of Medicine participated.

BOOK REVIEWS

FAMILIAL NON-REAGINIC FOOD ALLERGY. Arthur F. Coca, M.D. 2nd ed. 202 pages. 18 tables. 11 charts. Price $3.75. Springfield, Illinois: Charles C. Thomas, 1945.

The author has presented a concept of almost all non-infectious diseases that will, in succeeding years, either revolutionize the theory of a great part of medicine, or be buried in the files of "disproved after competent trial." To a very few who have given the time and thought necessary to the identification and elimination of allergenic substances, it seems that the author has justifiable enthusiasm for his contention.

The classification of allergic diseases is concisely reviewed, and especially is the "*idioblapsis*" or "familial non-reaginic" phase of food allergy forcefully presented as a new category of familial allergic diseases. The statement is made that the essential difference from the atopic category, is that this allergic reaction "practically always causes an acceleration of the pulse." A controversial issue arises here, since one must then assume that the cardiovascular mechanism is invariably sensitized. The author states that in ten years he has found no exception. Others believe they have found a rare exception. This is the new and necessary method of identifying the offending substance. Detailed explanation of the pitfalls one should expect to encounter in the use of this method, such as extraneous influences on the pulse rate, and especially "the latent period of lost sensitivity, recurrent reaction, major and minor reactions, depression of reactivity of shock tissue by single and rapidly repeated allergic reactions, sensitivity to a large number of important foods, and sensitivity to unavoidable inhalants, known or unknown," are given. This is the "meat" of the application of the "specific pulse reaction." Nearly all failures in this method may be traced to incomplete understanding of these chapters.

Biologic groupings of foods are given with a warning that few may be grouped as allergenic and that most must be tested separately.

Sympathectomy as an aid is considered, not only in its relation to hypertension, but as a valuable adjunct in other possible manifestations of allergy. From the author's experiences it diminishes not only the expressions of allergy, but in some cases entirely eliminates the expression. The physiological basis is not clear since it appears that the simple interruption of the autonomic pathway produces comparable results to more radical procedures. More complete knowledge of the entire function of the autonomics is necessary before this procedure will be used without hesitancy. Likewise, the mechanism of idioblaptic allergy is difficult of explanation, inasmuch as it is impossible to demonstrate a specific antibody. Similarly the histamine theory is held explanatory for the classification of allergens into major and minor groups, with the explanation that insufficient experimental work is available for a firm background.

Discussion, with pulse recordings on non-allergic individuals, is given in support of the author's contention that the human heart rate is remarkably constant no matter what the environmental influences. When any marked degree of variability occurs, allergic influence must be the primary consideration.

The relationship of idioblaptic allergy to hypertension, and its possible predisposing influence on the common cold are detailed with fair clinical and statistical evidences to support the conclusions arrived at. The coincidence of inconstant heart rate in those with carcinoma of the breast and in certain types of psychosis is also presented as suggestive evidence of a possible allergy factor. Obviously, years of clinical investigation will be required to furnish adequate proof of the relationship of these disorders.

M.G.M.

TRAUMA IN INTERNAL DISEASES. With Consideration of Experimental Pathology and Medicolegal Aspects. By Rudolf A. Stern, M.D., with a foreword by Francis Carter Wood, M.D. 575 pages, 20 chapters. Price $6.75. New York: Grune and Stratton, 1945.

The author has accomplished a difficult task well. Controversial medical testimonies are common when trauma is claimed as the cause of an internal disease rather than a surgical condition. Appreciating the necessity of a comprehensive knowledge of a vast, accumulating literature, both experimental and clinical, on the subject, which would be invaluable to the physician required to present sound medical testimony which aids justice in determining the truth, the writer has spared no effort to make available specific and detailed knowledge of the subject.

The chapters present an unbiased analysis of trauma in the etiology of internal diseases. Occupational diseases are not included in the scope of the book.

The increasing incidences of accidents and the rapid spread of accident insurance justifies a fair and thorough discussion of the development of all traumatic diseases as this text presents it.

Practitioners and specialists alike will find this book most valuable as a ready reference book when called upon to testify concerning possibility of trauma causing or aggravating internal diseases.

There is an exhaustive bibliography of forty-two pages. The book is well bound, the paper of good quality and the print very readable.

F.W.W.

SYMPTOMS OF VISCERAL DISEASE. Sixth Edition. By Francis Marion Pottenger, M.D. 442 pages. 87 illustrations, 10 color plates. Price $5.00. St. Louis: The C. V. Mosby Company, 1944.

The increasing interest in visceral neurology is attested by the appearance of a sixth edition of this remarkable text.

Symptoms of a reflex nature are sometimes most difficult to understand by the clinician because of their lack of understanding of the underlying physiologic mechanisms involved. The author attempts to correlate the clinical symptoms with clinical physiology in a manner which will help the physician to an accurate interpretation of the symptoms of visceral disease.

He describes the relationships between visceral and somatic conditions with neurons originating in the various cord segments. A better understandng of these segmental relationships and of the physiologic reflexes of visceral or somatic diseases is of inestimable value to the clinician. Although the author emphasizes the importance of reflexes, he broadly considers the physical, psychical, physiologic and pathologic influences which cause a variability of symptoms.

The monograph is arranged in three parts: Part I. The Vegetative Nervous System; Part II. The Relationship between the Vegetative Nervous System and the Symptoms of Visceral Disease; Part III. Innervation of Important Viscera with a Clinical Study of the More Important Viscerogenic Reflexes.

To the allergist the author's introductory remarks on the physical and psychic activities which change body control; the chapter on Subdermal Structures; and his discussion on page 171 of allergic inflammation are of particular interest.

However, the practical application of the principles of visceral neurology to the various diseases encountered in clinical medicine makes this monograph essential to the general practitioner as well as to all specialists who properly consider the human body as a unit.

The publishers should receive credit for the good binding, the fine paper stock and illustrations at a time when material and personnel were at a premium.

F.W.W.